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MEPROBAMATE AND OTHER AGENTS USED IN MENTAL DISTURBANCES

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CONTENTS

* This series of papers is the result of a conference on *Meprobamate and Other Agents Used in Mental Disturbances* held by The New York Academy of Sciences, Section of Biology and Psychology, on October 18 and 19, 1956.

Part III. Treatment of Psychiatric and Other Conditions with Meprobamate

Part IV. Use of Meprobamate in Muscle Spasm

Part I. Chemistry, Pharmacology, and Mode of Action of Meprobamate

INTRODUCTORY REMARKS

By Harry Beckman
Marquette University School of Medicine, Milwaukee, Wis.

While formerly we were naïvely at ease in the belief that, once we had drugs with which to treat successfully the symptoms of the mentally disturbed, all would become easy, I have now reached a more mature state of disillusionment through the realization that in this instance the mere manifestation of symptoms does not of necessity constitute disease. It is perfectly admissible to look upon the mentally ill person, properly so diagnosed, as a continuously diseased individual, even though there may be intervals during which he manifests none of the disease symptoms. It is important, also, to recognize the difference between this individual and the one who, while possessing essentially sound mental health, manifests only occasional symptoms of mental illness. As extreme examples of this latter type, I cite the three men characterized some years ago by Carl F. W. Ludwig as the Titans: Michelangelo, Rembrandt, and Beethoven. Throughout their lives, these three men were enigmatic, distrustful, and misanthropic; all were in continuous conflict with the world and, at times, they certainly crossed at least the borderline of madness.

It is my desire to emphasize the fact that the aberration underlying true mental illness may be quite a different thing from the imbalance that gives rise to occasional manifestations of the symptoms of the disease, and that our task is to devise remedial agents (curative or perhaps even prophylactic drugs) that will do more than merely enable us to control the symptoms. We need a therapy that will attack the etiological factors in mental illness, not merely behavioral disturbances such as those of the unconforming, embattled individual—disturbances that may be manifestations of genius. We must not be satisfied with drugs that merely reduce disturbed persons to a tranquil state. Such agents, applied indiscriminately, may ultimately eliminate from the race those periods of travail, turmoil, and stress out of which the supreme efforts of mankind have so often emerged.

The potentiality of mental illness exists in all of us (or rather in the best of us), and those urges that keep us frothing in our laboratories and at our desks when more sensible men are out fishing are perhaps the precious links with the "looney bin" that should not be severed. Evidences of imbalance, the symptoms of mental illness, are not the legitimate objectives of exclusive therapeutic endeavor, and the employment of tranquilizing agents on this level alone is loaded with potential doom for the race as the highest of evolved creatures. The etiological factors of overt mental illness are the only safe and proper objectives for treatment.

Furthermore, the tranquilizing agents, the recent advent of which has ushered in the brash era of psychopharmacology, are entirely specious in their claim to newness. Without the benefits of science or medicine, mankind has sought

peace through such agents for a truly venerable period of time. Throughout his history man has resorted to the use of alcohol; for nearly half a millennium he has indulged in tobacco. Pharmacology must do more than merely supply another such agent or another dozen such agents. It must supply the chemical tools with which to raise the hideous pall from the disease itself.

With this desirability in mind I suggest that, no matter how convincing the evidence presented here concerning the tranquilizing power of the new drugs may be, we must count as the highest achievements of the investigations reported in this monograph only those signs, however fragmentary and slight they may prove to be, of a mounting attack upon the deeply hidden etiological factors involved in mental illness.

THE HISTORY OF TENSION

By Aldous Huxley
Los Angeles, Calif.

The title of this paper is somewhat misleading for, strictly speaking, the history of tension does not exist. Tension is a form of disease; and diseases, as such, are beyond the scope of history. There is no such thing, for example, as a medieval stomach-ache, no such thing as a specifically neolithic focal infection, a characteristically Victorian neuralgia, or a New Deal epilepsy. So far as the patient is concerned, the symptoms of his illness are a completely personal experience, an experience to which the public life of nations, the events recorded in the headlines or discussed in scientific journals and literary reviews are totally irrelevant. Politics, culture, the march of civilization, all the marvels of nature, all the triumphs of art and science and technology—these things exist for the healthy, not for the sick. The sick are aware only of their private pains and miseries, only of what goes on within the four walls of the sickroom. For them the infinite universe has contracted almost to a point; nothing remains of it but their own suffering bodies, their own numbed or tormented minds. Disease as an actual experience is more or less completely independent of time and place. Consequently there cannot be a history of disease as experience; there can only be a history of medicine—that is to say, a history of theories about the nature of diseases and of the recipes employed at different times for their treatment, together with a history of the ways in which organized societies have reacted to the problems of disease within the community.

While tension, as a psychosomatic illness, has no history, at least some of the causes of tension lie within the public domain and can be made the subject of historical study. The same is true of the procedures sanctioned by various societies for the prevention and relief of tension. The subject is enormous; my time is short and my ignorance encyclopedic. I shall therefore make no attempt to discuss all the historical factors associated with tension, but shall confine myself to those that are most manageable and, at the same time, most relevant to the problems confronting us today.

Let me start with what I shall *not* talk about. I shall not talk, except perhaps incidentally, about the historical causes of tension. This would entail a discussion of two vast and complex themes—the transformation of culture patterns and the relations subsisting between a given culture and the individuals brought up within it.

At the risk of indulging in those Original Sins of the intellect, oversimplification and overabstraction, let me sum up this entire matter in one large, comprehensive generalization. Tension, I should say, arises in persons who, because of some congenital or acquired weakness, are unable to cope with certain distressing situations. These distressing situations are produced by

conflict—conflict between the fundamental drives to self-affirmation and sex on the one hand, and the equally fundamental drive to gregariousness on the other. The drive to gregariousness is canalized by society, sanctioned by tradition, and rationalized in terms of religion and philosophy; hence the intrusion of historical factors into a situation that, on the animal level, would be exclusively biological. The disease of tension seems to have arisen under all cultural conditions—in shame cultures as in guilt cultures, in primitive cultures no less than in highly developed cultures—and fundamentally similar devices for the relief of tension have been developed in all the societies of which we have any knowledge. It is with these devices for the relief of tension that I shall be concerned in this paper.

Like all other diseases, tension tends to narrow the patient's awareness until, in extreme cases, he is conscious of nothing but himself. Grave illnesses profoundly change the personality of their victims. To this changed personality the narrowing of awareness induced by the illness soon comes to seem almost normal and is taken for granted. Tension is not a severe illness, and those who suffer from tension are well enough to feel and suffer from the cramping self-centeredness imposed upon them by their psychosomatic disorder. They are like those lost souls whose punishment is, in the words of the great Catholic poet, Gerard Manley Hopkins, "to be their sweating selves, but worse." The victim of tension knows and is acutely distressed by this sense of being his sweating self, but worse. And here we may remark that even healthy people are often distressed by the realization that they are condemned to be the separate, insulated individuals they so irretrievably are. Neurotics hate being their sweating selves, but worse. Normal people hate being their sweating selves, period. One of the most disagreeable symptoms of tension is simply the normal distress at being an island universe raised, so to speak, to a higher power. Man is a self-adoring egotist, but an egotist who often feels an intense distaste for the object of his idolatrous worship. Correlated with this distaste for the beloved self, there exists in all human beings an urge to self-transcendence, a wish to escape from the prison of personality, a longing to become something other and greater than the all-too-familiar Me, a susceptibility to nostalgia for a world superior to, or at least different from, the boring or painful universe of everyday reality. The religious man has attributed this universal urge to self-transcendence to an innate and deep-seated yearning for the divine. The biologist sees the matter somewhat differently, and he attributes man's desire for self-transcendence to the workings of his innate gregariousness. The individual longs to be merged with the herd, but he is too self-centered to be able to do so completely and too self-conscious to be able to sustain the attempt for long. He is therefore condemned to live in a state of chronic dissatisfaction, constantly pining for something that, in the very nature of things, he can never have.

These two explanations are not mutually exclusive, and I should be inclined to think that both are partially correct. Be that as it may, the facts for which they profess to account are genuine facts. There *is* an urge to self-transcendence and, with it, a profound distaste for the insulated ego, a distaste which, in the victims of tension, becomes acute and agonizing. In every human

culture certain procedures for achieving temporary self-transcendence, and thereby relieving tension, have been developed and systematically employed. These procedures may be classified under a few comprehensive headings. There are the chemical methods, the musical and gymnastic methods, the methods that depend on the subjection of insulated individuals to the influence of crowds, the various religious methods and, finally, the methods whose purpose is mystical self-transcendence—the various yogas and spiritual exercises of Oriental and Western tradition. Hours would be needed to do justice to all these stratagems, and I must limit myself to a discussion of only two of them, the most popular and the most difficult to control, namely, the chemical method and what may be called the crowd method.

This monograph is concerned with the use of certain chemical compounds that produce certain changes of consciousness and so permit a measure of self-transcendence and a temporary relief of tension. These tranquilizing drugs are merely the latest additions to a long list of chemicals that have been used from time immemorial for changing the quality of consciousness, thus making possible some degree of self-transcendence and a temporary release from tension. Let us always remember that, while modern pharmacology has given us a host of new synthetics, it has made no basic discoveries in the field of the natural drugs; it has merely improved the methods of extraction, purification, and combination. All the naturally occurring sedatives, narcotics, euphorics, hallucinogens, and excitants were discovered thousands of years ago, before the dawn of civilization. This surely is one of the strangest facts in that long catalogue of improbabilities known as human history. It is evident that primitive man experimented with every root, twig, leaf, and flower, every seed, nut, berry, and fungus in his environment. Pharmacology is older than agriculture. There is good reason to believe that even in paleolithic times, while he was still a hunter and a food-gatherer, man killed his animal and human enemies with poisoned arrows. By the late Stone Age he was systematically poisoning himself. The presence of poppy heads in the kitchen middens of the Swiss Lake Dwellers shows how early in his history man discovered the techniques of self-transcendence through drugs. There were dope addicts long before there were farmers.

Here let me mention a fact of some importance. To relieve tension, a chemical compound need not have the characteristics of a tranquilizer. Alcohol, for example, is far from tranquilizing, at least in the middle stages of intoxication, and it has been relieving tension ever since Noah made his epoch-making discovery. Self-transcendence can be achieved by an excitant as well as by a narcotic or a hallucinogen. Tension is relieved not only by such contemplative drugs as opium, peyote, kava, and ayahuasca, but also by active, extraverted intoxicants such as wine, hashish, and the soma of ancient India. Physiologically and socially, some drugs are much less harmful than others, and are therefore to be preferred, although such merely utilitarian considerations have never carried much weight with the drug taker. For him anything that produces a measure of self-transcendence and release seems good. So long as it works here and now, who cares what may happen later on?

In his *Varieties of Religious Experience* William James says: "The sway of

alcohol over mankind is unquestionably due to its power to stimulate the mystical faculties of human nature, usually crushed to earth by the cold facts and dry criticisms of the sober hour. Sobriety diminishes, discriminates and says no; drunkenness expands, unites and says yes. It is in fact the great exciter of the *Yes* function in man. It brings its votary from the chill periphery of things to the radiant core. It makes him for the moment one with truth. Not through mere perversity do men run after it. To the poor and the unlettered it stands in the place of symphony concerts and of literature. It is part of the deeper mystery and tragedy of life that whiffs and gleams of something that we immediately recognize as excellent should be vouchsafed to so many of us only in the fleeting earlier stages of what in its totality is so degrading a poison. The drunken consciousness is one bit of the mystic consciousness, and our total opinion of it must find its place in our opinion of that larger whole."

Elsewhere in the *Varieties* James cites the dictum of one of his medical friends: "There is no cure for dipsomania except religiomania." In their somewhat too epigrammatic way, these words express a truth that the collective experience of Alcoholics Anonymous has amply confirmed. Mystical experience stands to drunkenness in the relation of whole to part, of health to sickness. For the alcoholic as for the mystic there is an opening of doors, a bypassing of what I have called the cerebral reducing valve, the normal brain function that limits our mental processes to an awareness, most of the time, of what is biologically useful. For both there is a glimpse of something transcendent to the world of everyday experience—that narrow, utilitarian world that our self-centered consciousness selects from out of the infinite wealth of cosmic potentialities. What the drunkard sees in the earlier phases of intoxication is immediately recognized as excellent. What is not excellent is the particular method employed for achieving this transcendental experience.

Alcohol is one of the oldest and certainly the most widely used of all consciousness-changing drugs. Unfortunately it is a rather inefficient and, at the same time, a rather dangerous drug. There are other and better ways than getting drunk for achieving the same intrinsically excellent results. Some of these ways are chemical, others are psychological. Others involve fasting, voluntary insomnia, and various forms of self-torture. All these procedures modify the normal body chemistry and so facilitate the bypassing of the cerebral reducing valve and the achievement of a temporary escape from the prison of insulated selfhood. Some day, when psychology becomes a genuine science, all these traditional methods for producing self-transcendence will be systematically examined, and their respective merits and defects will be accurately assessed. For the present we must be content with such fragmentary knowledge as is now available.

William James's characterization of alcohol as an exciter of the mystical faculties is strikingly confirmed by what the mystics themselves have said of their ecstatic experiences. In the mystical literature of Islam, metaphors derived from wine and winebibbing are constantly employed. Precisely similar metaphors are to be found in the writings of some of the greatest Christian saints. Thus St. John of the Cross calls his soul *la interior bodega di*

mi Amado—the inward wine cellar of my Beloved. And St. Teresa of Avila tells us that she "regards the center of our soul as a cellar, into which God admits us when and as it pleases Him, so as to intoxicate us with the delicious wine of His grace."

The experience of self-transcendence and the release of tension produced by alcohol and the other consciousness-changing chemicals is so wonderful, so blessed and blissful, that men have found it quite natural to identify these drugs to which they owe their momentary happiness with one or other of their gods. "Religion," said Karl Marx, "is the opium of the people." It would be at least as true to say that opium is the religion of the people. A few mystics have compared the state of ecstasy to drunkenness; but innumerable drinkers, smokers, chewers, and snuff-takers have achieved a form of ecstatic release through the use of drugs. The supernatural qualities of this mental state are projected outward upon the drugs that produced it. Thus, in Greece wine was not merely sacred to Dionysus; wine *was* Dionysus. Bacchus was called Theoinos—Godwine—a single word equating alcohol with deity, the experience of drunkenness with the holy spirit. "Born a god," said Euripides, "Bacchus is poured out in libations to the gods, and through him men receive good." That good, according to the Greeks, was of many kinds—physical health, mental illumination, the gift of prophesying, the ecstatic sense of being one with divine truth. Similarly, in ancient India, the juice of the soma plant (whatever that plant may have been) was not merely sacred to Indra, the hero-god of battles; it *was* Indra. And at the same time it was Indra's *alter ego*, a god in its own right. Many similar examples of this identification of a consciousness-changing drug with some god of the local pantheon could be cited. In Siberia and Central America various species of hallucinogenic mushrooms are regarded as gods. The Indians of the southwestern United States identified the peyote cactus with native deities and, in recent years, with the Holy Ghost of Christian theology. In classical times the northern barbarians who drank malt liquor worshiped their beer under the name of Sabazius. Beer was also a god for the Celtic peoples, as mead seemed divine to the Scandinavians and the Teutons. In Anglo-Saxon, the idea of catastrophe, of panic, of the ultimate in horror and disaster is conveyed by a word whose literal meaning is "the deprivation of mead." Almost everywhere the consumption of consciousness-changing drugs has been associated, at one time or another, with religious ritual. Drinking, chewing, inhaling, and snuff-taking have been regarded as sacramental acts, sanctioned by tradition and rationalized in terms of the prevailing theology. In the Moslem world alcohol was forbidden, but the urge to self-transcendence could not be suppressed, and there were and still are places within the Moslem world where the consumption of *Cannabis indica* is not only sanctioned by society, but has even been turned into a kind of religious rite. Certain Mohammedan authors have seen in hashish the equivalent of the sacramental bread and wine of the Christians. Among the Jews many efforts were made to give a religious sanction to winebibbing. Jeremiah refers to the "cup of consolation," which was administered to the bereaved. Amos speaks of men who drink wine in the house of their God. Micah has some harsh words for those who, in his day, used to prophesy under the in-

fluence of alcohol. Isaiah denounces the priests and prophets who have "erred through strong drink." They have erred, he says, "in vision." Traditionally, Dionysus was the god of prophecy and inspiration; but alas, the revelations of alcohol are not altogether reliable.

From self-transcendence by chemical means we now pass to self-transcendence by social means. The individual makes direct contact with society in two ways—as a member of some familial, professional, or religious group, or as a member of a crowd. A group is purposive and structured; a crowd is chaotic, serves no particular purpose, and is capable of anything except intelligent action. Using an analogy that is not too misleading, we can say that the first is an organ of the body politic, the second is a kind of tumor, generally benign, but sometimes horribly malignant. The greater part of most people's lives is passed in groups. Participation in crowd activities is a relatively rare event. This is fortunate, for individuals in a crowd are different from, and in every respect worse than, individuals in isolation or within purposive and organized groups. A man in a crowd loses his personal identity, and that, of course, is why he likes to be in a crowd. Personal identity is what he longs to transcend, what he desires to escape. Unfortunately, the members of a crowd lose more than their personal identity; they also lose their powers of reasoning and their capacity for moral choice. Their suggestibility is increased to the point where they cease to have any judgment or will of their own. They become very excitable, lose all sense of individual or collective responsibility, are subject to sudden and violent accesses of rage, enthusiasm, and panic, and become capable of performing the most monstrous, the most completely senseless acts of violence—usually against others, but sometimes against themselves. In a word, a man in a crowd behaves as though he had swallowed a large dose of some powerful intoxicant. He is a victim of what may be called herd poisoning. Like alcohol, herd poison is an active, extraverted drug. It changes the quality of individual consciousness in the direction of frenzy, and makes possible a high degree of downward self-transcendence. The crowd-intoxicated individual escapes from insulated selfhood into a kind of subhuman mindlessness.

From the beginning men have done their work and gone through the serious business of living in purposeful groups. Crowds have provided them with their psychological vacations. Nourishment drawn from the group has been their staple food; herd poison has been their delicious dope. Religion has everywhere sanctioned and rationalized intoxication by herd poison, just as it has sanctioned and rationalized the use of consciousness-changing chemicals. Alfred North Whitehead's statement that "religion is what the individual does with his solitariness" is true only if we choose to define religion as something that, as a matter of historical fact, it has never been, except for a small minority. And the same would be true of a definition of religion in terms of what the individual does with his experience of being in a small, dedicated group such as the Quaker Meeting or the "two or three gathered together in my name," of whom Christ spoke in the gospel. The spirituality of small groups is a very high form of religion, but it is not the only or the commonest form—it is merely the best. Significantly enough, Christ promised to be in the midst of a group of two or three. He never promised to be present in a crowd. Where two or

three thousand, or two or three tens of thousands are gathered together, the indwelling presence is generally of a very different and un-Christlike kind. Yet such crowd activities as the mass revival meeting and the pilgrimage are sanctioned and even actively encouraged by religious leaders today just as they were in the pagan past. The reason is simple. Most people find it easier to achieve self-transcendence and relief from tension in a crowd than in a small group or when they are by themselves. These herd poisonings in the name of religion are not particularly beneficial; they merely provide brief holidays from insulated self-consciousness.

The history of man's efforts to find self-transcendence in crowds is long and, for all its strangeness, its weird aberrations, profoundly monotonous. From the potlatch and the corroboree to the latest outburst of "rock 'n roll," the manifestations of herd poisoning exhibit the same subhuman characteristics. At their best, such performances are merely grotesque in their subhumanity; at their worst, they are both grotesque and horrible. One thinks, for example, of the festivals of the Syrian goddess, in the course of which, under the maddening influence of herd poison and priestly suggestion, men castrated themselves and women lacerated their breasts. One thinks of Greek maenadism, with its savage dismemberment of living victims. One thinks of the Roman saturnalia. One thinks of all the outbursts of crowd intoxication during the Middle Ages—the children's crusades, the periodical orgies of collective flagellation, and those strange dancing manias in which self-transcendence through herd poisoning was combined with self-transcendence by gymnastic means and self-transcendence through repetitive music. One thinks of the wild religious revivals, the frantic stampedes of those who believed that the end of the world was at hand, the frenzies of iconoclasm in the name of God, of senseless destruction for righteousness' sake. These are bad enough, but there is something much worse—the crowd intoxication that is exploited by the ambitious rabble-rouser for his own political or religious ends.

In the spring of 1954, while I was staying at Ismailia on the Suez Canal, I was taken by my hosts to the local movie theater. The film, which was drawing record crowds, was *Julius Caesar* played in English, but with Arabic subtitles. The spectators sat in spellbound attention, their eyes riveted on the screen. Why on earth, I kept wondering, should twentieth-century Arabs be so passionately interested in a sixteenth-century Englishman's account of events that had taken place at Rome in the first century B.C.? And suddenly it was obvious. Caesar, Brutus, Antony, all those upper-class politicians fighting for power and, in the process, cynically flattering and exploiting a proletarian mob they despised but could not do without, were thoroughly familiar and contemporary figures to the Egyptian audience. What had happened in Rome just before and after Caesar's murder was very like what had been happening only a few weeks before in Cairo when Naguib fell, rose again in triumph, and was once more brought low by a rival who knew how to play on the passions of the crowd, how to make use of its drunken enthusiasm and drunken violence for his own purposes. Looking at Shakespeare's play, the moviegoers of Ismailia found themselves looking at an uncensored report on the latest *coup d'état.*

Of course, the greatest virtuoso in the art of exploiting the symptoms of herd poisoning was Adolf Hitler. The Nazis did their work with scientific thoroughness. All the resources of modern technology were mobilized in order to reduce the greatest possible number of people to the lowest possible state of downward self-transcendence. Phonographs repeated slogans. Loudspeakers poured forth the brassy and strongly accented music, the repetition of which drives people out of their minds. Concealed sound machines produced subsonic vibrations at the critical, soul-stirring rate of fourteen cycles per second. Modern methods of transportation were used to assemble thousands of the faithful under the floodlights in enormous stadiums, and the voice of the arch-hypnotist was broadcast by radio to millions more.

"Bliss was it in that dawn to be alive." So wrote Wordsworth of his experience of herd poisoning in the first, joyful months of the French Revolution. In our own time, millions of men and women, millions of enthusiastic boys and girls have had a similar experience. For the herd-poisoned members of the mobs that are used for the making of revolutions and the buttressing of dictatorial power, the dawn even of Nazism, even of Communism, seems blissful. Unfortunately, dawns are succeeded by laborious and often unpleasant days and evenings. In those later hours of revolutionary history, bliss is apt to be conspicuous by its absence. At the moment of sunrise, however, nobody ever thinks of what is likely to happen in the afternoon. Like alcoholics or morphine addicts, the victims of herd poison are interested only in releasing self-transcendence here and now. "After me the deluge," is their motto. And sure enough, the deluge punctually arrives.

From the history of tension let us turn, in conclusion, to the present and the future. It is clear, I think, that the problem of tension will be completely solved only when we have a perfect society—that is to say, never. Meanwhile, it always remains possible to find partial solutions and temporary palliatives. Let us consider a few practical steps that it would be fairly easy to take.

First of all we might incorporate into our present profoundly unsatisfactory and disappointing system of education a few simple courses in the art of controlling the autonomic nervous system and the subconcious mind. As things now stand, we teach children the principles of good health, good morals, and good thinking, but we do not teach them how to act upon these principles. We urge them to make good resolutions, but we do nothing whatever to help them carry these resolutions into practice. A main source of tension is the consciousness of miserably failing to do what we know we ought to do. If every child were given some training in what Hornell Hart has called autoconditioning, we should do more for general decency and good feeling than all the sermons ever preached.

The next step to be taken is prophylactic in character. Human beings pine for self-transcendence, and getting drunk on herd poison is one of the most effective methods of taking a holiday from insulated selfhood and the burdens of responsibility. So long as they indulge in crowd-intoxication at football games and carnivals, at revival meetings and the rallies of democratically organized political parties, no harm is done. We must never forget, however, that the spellbinders, the rabble-rousers, the potential Hitlers are always with

us. We must never forget that it is very easy for such men to turn an innocent orgy into an instrument of destruction, into a savage, mindless force directed toward the overthrow of liberty. To prevent them from exploiting crowd intoxication for their own sinister purposes we must be perpetually on our guard. Whether a world inhabited by potential Hitlers on the one hand and potential herd-poison addicts on the other can ever be made completely safe for rationality and decency seems doubtful, but at least we can try to make it a little safer than it is at present. For example, we can give our children lessons in the elements of general semantics. We can tell them about the frightful dangers of intellectual sin. We can make their flesh creep by reciting to them the disastrous consequences to societies and to individuals of the rabble-rouser's oversimplification, overgeneralization, and overabstraction. We can remind them to live in present time and to think concretely and realistically, in terms of observable fact. We can unveil the absurd and discreditable secrets of propaganda and illustrate our lectures with examples drawn from the history of politics, religion, and the advertising industry. Would such a training be effective? Perhaps—or perhaps not. Herd poison is a very powerful intoxicant. Once they get into a crowd, even upright and sensible men are apt to lose their reason and accept all the suggestions, however nonsensical or however immoral, that may be given them. All we can hope to accomplish is to make it more difficult for the rabble-rouser to do his nefarious work.

The third step we must take will, in fact, be taken whether we like it or not. Once the seeds of a science have been planted they tend to sprout and develop autonomously according to the law of their own being, not according to the laws of *our* being. Pharmacology has now entered upon a period of rapid growth, and it seems quite certain that in the next few years scores of new methods for changing the quality of consciousness will be discovered. So far as the individual human being is concerned, these discoveries will be more important, more genuinely revolutionary, than the recent discoveries in the field of nuclear physics and their application to peacetime uses. If it does not destroy us, nuclear energy will merely give us more of what we have already—cheap power, with its corollary of more gadgets, larger irrigation projects, and more efficient transportation. It will give us these things at a very high price—an increase in the amount of noxious radiation, with its corollaries of harmful mutations and a permanent fouling of man's genetic pool. But the pharmacologists will give us something that most human beings have never had before. If we want joy, peace, and loving kindness, they will give us loving kindness, peace, and joy. If we want beauty, they will transfigure the outside world for us and open the door to visions of unimaginable richness and significance. If our desire is for life everlasting, they will give us the next best thing—aeons of blissful experience miraculously telescoped into a single hour. They will bestow these gifts without exacting the terrible price that, in the past, men had to pay for resorting too frequently to such consciousness-changing drugs as heroin or cocaine, or even that good old stand-by alcohol. Already we have at our disposal hallucinogens and tranquilizers whose physiological price is amazingly low, and there seems to be every reason to believe that the consciousness-changers and tension-relievers of the future will do their work even more

efficiently and at even lower cost to the individual. Human beings will be able to achieve effortlessly what in the past could be only achieved with difficulty, by means of self-control and spiritual exercises. Will this be a good thing for individuals and for societies? Or will it be a bad thing? These are questions to which I do not know the answers. Nor, may I add, does anyone else. The outlines of these answers may begin to appear a generation from now. Meanwhile, all that one can predict with any degree of certainty is that it will be necessary to reconsider and re-evaluate many of our traditional notions about ethics and religion, and many of our current views about the nature of the mind, in the context of the pharmacological revolution. It will be extremely disturbing; but it will also be enormous fun.

THE CHEMISTRY AND MODE OF ACTION OF TRANQUILIZING DRUGS

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Recently a group of therapeutic agents called "tranquilizers" has been introduced into medicine. This word, which is interchangeable with the term "ataraxics," is used to describe agents that quiet seriously disturbed psychotics, cause remission of schizophrenic and paranoic symptoms, bring peace of mind to overwrought neurotics, or antagonize the manifestations of hallucinogenic agents. In this article the chemical structure and pharmacological properties of tranquilizers are discussed. The properties common to all tranquilizers were sought and the differences among them were studied. It was found that all available tranquilizers could be divided into two broad classes, differing from each other in their pharmacological properties, their mode of action, and their clinical usefulness.

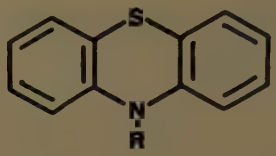
The Chemical Structure of Tranquilizers

According to their chemical structure, the most important tranquilizers can be classified in the following four groups: (1) compounds derived from phenothiazine; (2) reserpine and related alkaloids such as deserpidine and rescinnamine; (3) compounds derived from diphenylmethane; and (4) compounds derived from substituted propanediols such as meprobamate, mephenesin, and 2-substituted 4-hydroxymethyl 1,3-dioxolanes.

(1) *Compounds derived from phenothiazine.* FIGURE 1 gives the name and chemical structure of certain phenothiazines that have been used in medicine. Of those to which tranquilizing properties have been ascribed, chlorpromazine (Thorazine), promazine (Sparine), mepazine (Pacatal), procloperazine (Compazine), and NP-207 (Kinross-Wright, 1956) are perhaps the most important. A few of the other derivatives of phenothiazine that have been used in medicine for other purposes are also listed. Phenothazine, itself, was popular for a time as an insecticide and an anthelmintic, but its use was abandoned because it sometimes caused blood dyscrasias and toxic hepatitis (Bercovitz *et al.*, 1943; Hubble, 1941). Promethazine (Phenergan) is used chiefly as an antihistaminic, and diethazine (Diparcol) and ethopropazine (Parsidol) are employed chiefly as anti-parkinsonian agents. Some of these or related agents may yet be introduced as tranquilizers.

(2) *Reserpine and related alkaloids such as deserpidine and rescinnamine.* These substances liberate 5-hydroxytryptamine (serotonin) in the brain (Brodie *et al.*, 1955). Reserpine also shows some structural resemblance to 5-hydroxytryptamine (Woolley and Shaw, 1954). In addition, yohimbine is chemically closely related to reserpine.

(3) *Compounds derived from diphenylmethane.* The tranquilizers azacyclonol (Frenquel), benactyzine (Suavitil), and hydroxyzine (Atarax) belong to this group (FIGURE 2). A therapeutic agent for which tranquilizing properties



R		
H	XL-50	PHENOTHIAZINE
$-CH_2CH_2N(C_2H_5)_2$	DIETHAZINE	DIPARCOL
$-CH_2CH(CH_3)N(C_2H_5)_2$	ETHOPROPAZINE	PARSIDOL
$-CH_2CH(CH_3)N(CH_3)_2$	PROMETHAZINE	PHENERGAN
$-CH_2CH_2N$	PYRATHIAZINE	PYRROLAZOTE
$-CH_2$ N-CH_3	MEPAZINE	PACATAL
$-CH_2CH_2CH_2N(CH_3)_2$	PROMAZINE	SPARINE
$-CH_2CH_2CH_2N(CH_3)_2$ (2-Cl)	CHLORPROMAZINE	THORAZINE
$-CH_2CH_2CH_2N$ NCH$_3$ (2-Cl)	PROCLOPERAZINE	COMPAZINE
$-CH_2CH_2$ H CH_3 (2-Cl)	—	NP-207

FIGURE 1. Chemical structure of various phenothiazines used in medicine.

have not yet been claimed is the antispasmodic adiphenine (Trasentine), which is closely related to benactyzine. The antiemetic, meclizine (Bonamine), and the antihistaminic, chlorcyclyzine (Perazil), are closely related to hydroxyzine. All these compounds have a chemical structure related to β-diethylaminoethyl diphenylpropylacetate (SKF 525-A), which has been shown to inhibit the enzymatic breakdown of a variety of drugs (Axelrod *et al.*, 1954).

(4) *Compounds derived from substituted propanediols such as meprobamate (Equanil and Miltown), mephenesin (Tolserol and Mephate), and 2-substituted 4-hydroxymethyl 1,3-dioxolanes such as Glyketal* (Berger, 1949a) *and Dimethylane.* The structural formulas of these are given in FIGURE 3.

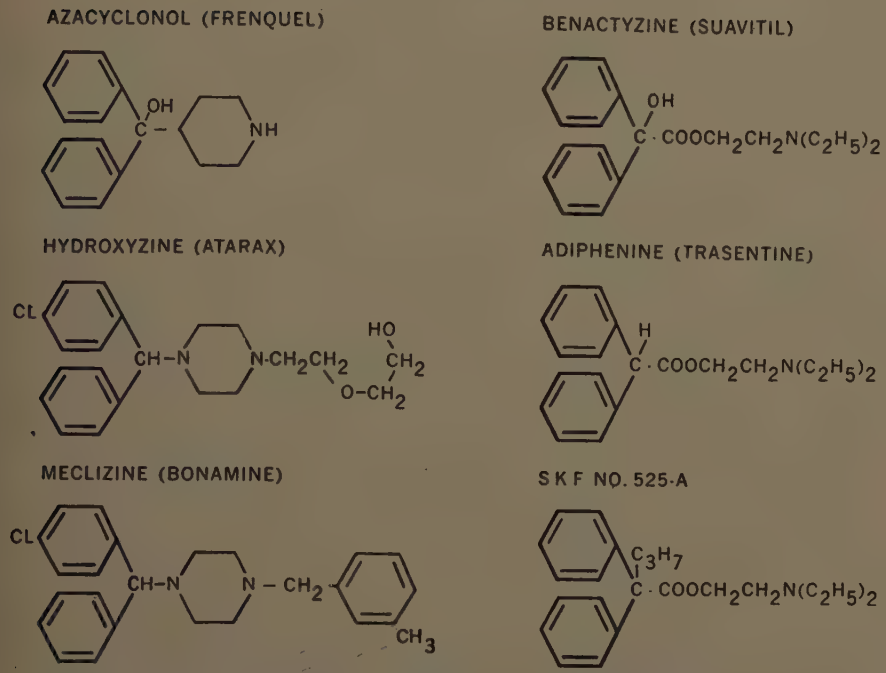


FIGURE 2. Chemical structure of tranquilizers and other chemicals derived from diphenylmethane.

The Pharmacology of Tranquilizers

Up to the present time no pharmacological test has been developed in which all drugs used as tranquilizers show a positive response. In the pretranquilizer era these drugs would have been classified differently in accordance with some of their other pronounced and useful pharmacological actions.

Chlorpromazine would have been called a potent hypnotic. In mice, as little as 7 mg./kg. injected intraperitoneally produces anesthesia. Many

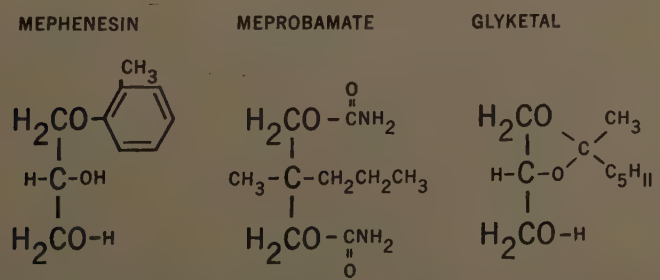


FIGURE 3. Chemical structure of mephenesin, meprobamate, and Glyketal, drawn to demonstrate the chemical relationship.

barbiturates must be given in somewhat larger doses to produce anesthesia of equivalent depth. In humans, under strictly controlled conditions, it has been demonstrated that 200 mg. of secobarbital sodium (Seconal) does not cause impairment of performance significantly greater than chlorpromazine given in similar amounts (Kornetsky, 1956).

Reserpine would have been considered a true sedative. Even in small doses, the drug strikingly reduces the spontaneous activity of animals, but it does not produce anesthesia or loss of the righting reflex even in very large doses.

Benactyzine would have been considered an atropine substitute and a spasmolytic, and hydroxyzine would have been regarded as a potent antihistaminic. Both drugs produce in animals some hyperexcitability that may lead to tremors and convulsions after doses of about 80 mg./kg. or more. Meprobamate would have been called a long-acting muscle relaxant and anticonvulsant. In large doses, meprobamate produces reversible paralysis of most voluntary muscles without embarrassing respiration.

There are, however, several testing procedures, according to which tranquilizers can be divided into two broad classes. These are as follows.

(1) *Taming effect on monkeys.* When given to rhesus monkeys, many tranquilizers produce a condition often described as "taming." In suitable doses, chlorpromazine and reserpine produce a state of tranquility characterized by a loss of interest in the environment, a loss of interest in food, and catatonia (Das *et al.*, 1954). The animals do not attack spontaneously, and sit motionless, paying little attention to their surroundings. They are in full control of their muscular powers and occasionally may carry out a vicious attack in response to mild stimulation or a slight movement by the experimenter. After they have received an intravenous injection of hydroxyzine, their behavior is similar to that observed after the administration of chlorpromazine. After oral administration of hydroxyzine, however, no behavioral changes are observable. Benactyzine is similar and perhaps somewhat less effective than hydroxyzine in producing this state (Hendley *et al.*, 1956).

The picture seen after the administration of meprobamate is quite different. The animals lose all aggressiveness, but they do not show listlessness or catatonia. They are playful, eager to accept food, and interested in their environment (Berger, 1954; Berger *et al.*, 1956a).

(2) *Effect on isolated intestine.* The ability of tranquilizers and related substances to prevent contractions produced by acetylcholine and serotonin (5-hydroxytryptamine) was evaluated, using the rat colon as test object. The ability of drugs to antagonize histamine was evaluated on the isolated guinea pig ileum. A segment of the intestine was suspended in a bath in Ringer's solution at 37° C. The stimulant drugs were used in doses that produce submaximal contractions as follows: acetylcholine chloride 5 γ/100 ml., 5-hydroxytryptamine creatine sulfate 10 γ/100 ml., and histamine diphosphate 50 γ/100 ml. After several reproducible contractions were obtained, the drugs were added and allowed to remain in the bath for 3 min. before addition of the stimulant. The results of these tests are given in TABLE 1.

Meprobamate is the only drug that does not exert an appreciable antispasmodic effect against any of the stimulants. All other drugs tested exhibit a

TABLE 1

CONCENTRATIONS OF AGENTS* REQUIRED TO PREVENT CONTRACTION OF ISOLATED SMOOTH MUSCLE STIMULATED BY ACETYLCHOLINE, SEROTONIN, OR HISTAMINE

	Acetylcholine	Serotonin	Histamine
Chlorpromazine	0.5	0.5	1.0
Reserpine	4.0	4.0	2.5
Benactyzine	0.05	1.0	5.0
Hydroxyzine	8.0	0.25	0.1
Diphenhydramine	0.5	1.25	0.1
Meprobamate	100.0	100.0	100.0

* In γ/ml.

marked antispasmodic action against at least one of the stimulants. Chlorpromazine and reserpine appear to show little selectivity and have similar potency in relieving spasms produced by acetylcholine, serotonin, or histamine. Hydroxyzine is a very potent histamine antagonist, equivalent in this respect to diphenhydramine (Benadryl). Hydroxyzine also possesses good antiserotonin action, but is a relatively poor acetylcholine antagonist. Benactyzine is an outstanding antispasmodic when acetylcholine is used as the stimulant and, in this respect, is similar to its chemical relative, adiphenine (Trasentine). Benactyzine also possesses appreciable antiserotonin action, but is a relatively poor histamine antagonist.

(3) *Prolongation of hexobarbital anesthesia.* Winter (1948) has shown that certain antihistaminics that do not exert a hypnotic action in animals will prolong the hypnotic and anesthetic effects of hexobarbital. It has been shown previously that many tranquilizers have a similar prolonging effect on hexobarbital anesthesia (Berger *et al.*, 1956b). These results are illustrated in TABLE 2.

Groups of mice were given hexobarbital sodium 100 mg./kg. intraperitoneally. Other drugs, with the exception of reserpine, were given simultaneously, also by the intraperitoneal route in doses indicated in the table. Reserpine, because of its slow onset of action, was given 1 hour prior to hexobarbital sodium. Controls receiving hexobarbital sodium only were run each

TABLE 2

PROLONGATION OF HEXOBARBITAL ANESTHESIA IN MICE BY VARIOUS SUBSTANCES

All Drugs Were Given Intraperitoneally Together with Hexobarbital Sodium 100 mg./kg., Except Reserpine, Which Was Given 1 Hour Prior to Hexobarbital

Drug	Dose, mg./kg.	Increase over controls, per cent	t	P
Chlorpromazine	2.5	103	3.6	0.005
Reserpine	5.0	171	10.0	<0.001
Benactyzine	20.0	123	8.8	<0.001
Hydroxyzine	20.0	108	7.4	<0.001
Diphenhydramine	20.0	66	3.4	0.003
SKF 525-A	2.5	68	2.7	0.015
Meprobamate	20.0	−3	0.2	0.85

day the experiments were performed. The length of time during which the righting reflex was lost was measured and taken as the duration of anesthesia.

At least 10 mice were used at each dose level. Of the compounds mentioned in the table, only chlorpromazine and meprobamate are capable of producing a loss of righting reflex when given by themselves in suitable dosage.

All tranquilizers produce prolongation of hexobarbital anesthesia, and all except meprobamate will do so when given in low doses. In the case of the tranquilizers derived from diphenylmethane, the mechanism of action may well be similar to that observed after administration of SKF 525-A, to which these tranquilizers and diphenhydramine have a marked structural resemblance. Axelrod *et al.* (1954) have shown that SKF 525-A inhibits the enzymatic breakdown of hexobarbital, and it may well be that these structurally related compounds act similarly. Chlorpromazine also may act as an enzyme inhibitor, or there may be true synergism of the central depressant properties of the two agents. Meprobamate in sufficiently large doses will also prolong hexobarbital anesthesia by a synergistic action, but this effect appears to be quite different from that observed after administration of the diphenylmethane tranquilizers, because the latter do not cause loss of the righting reflex when given by themselves.

(4) *Increase in strychnine toxicity.* Sherman (1956) has recently shown that the toxicity of strychnine is increased in animals pretreated with diphenhydramine. It was of interest to see whether tranquilizers would act like diphenhydramine in increasing the toxicity of strychnine. Jenney (1954), Chen *et al.* (1954), and Berger *et al.* (1956b) have previously shown that certain tranquilizers lower the electroshock seizure threshold.

These experiments were carried out by a technique similar to that used by Sherman. The tranquilizers were given subcutaneously to mice, and strychnine was administered by the intraperitoneal route 25 min. later in a dose of 1.5 mg./kg. Controls (receiving strychnine only) were run concurrently with each experiment, and at least 20 animals were used for each compound. TABLE 3 gives the results of these experiments, and it shows that all tranquilizing

TABLE 3

EFFECT OF VARIOUS SUBSTANCES ON THE INCIDENCE OF DEATH PRODUCED BY STRYCHNINE 1.5 mg./kg. INTRAPERITONEALLY

All Drugs Were Given Subcutaneously 25 Minutes Before the Administration of Strychnine, Except Reserpine, Which Was Given 3 Hours Prior to Strychnine

Drug	Dose, mg./kg.	Increase in deaths over controls, per cent	χ^2	P
Chlorpromazine	10	82	11.52	<0.001
Reserpine	5	90	85.26	<0.001
Benactyzine	20	325	52.75	<0.001
Hydroxyzine	20	110	15.86	<0.001
Diphenhydramine	20	114	28.04	<0.001
SKF 525-A	5	67	6.67	0.01
Atropine	20	267	27.09	<0.001
Meprobamate	80	−10	0.21	0.54

drugs with the exception of meprobamate increased the toxicity of strychnine. The enzyme inhibitor SKF 525-A and atropine produced the same result. Meprobamate, in doses of 80 mg./kg., had no significant effect. Higher doses of meprobamate protected all animals from strychnine deaths.

(5) *Effect on the electroencephalogram.* The effects of various tranquilizers on the electrical activity of the brain have recently been reported by Berger *et al.* (1957). In these experiments recordings were made in curarized cats and rhesus monkeys using monopolar cortical electrodes and bipolar concentric electrodes for subcortical recordings. All drugs were injected intravenously.

Chlorpromazine, hydroxyzine, and benactyzine in suitable doses produced a high-voltage slow-activity pattern characteristic of a sleep record. These changes were observed in all leads and showed little selectivity (FIGURES 4 and 5). Administration of atropine and scopolamine produced similar sleep changes, as previously observed by Rinaldi and Himwich (1955) and by Longo (1956). Reserpine appeared to act similarly, but could not be thoroughly evaluated because of the difficulties encountered in the preparation of the drug in an injectable form and because of the well-known slow onset of action of the drug.

Meprobamate produced characteristic changes that were quite different from those obtained after the administration of other tranquilizers (Hendley *et al.*, 1954). After low doses there were no changes in cortical or subcortical leads, with the exception of those taken from the nucleus ventralis lateralis of the thalamus, which showed a high-voltage slow record (FIGURE 6). Frequent waxing and waning and occasional isolated spindling appeared. After large doses, changes in other leads also became apparent. These consisted of generalized slowing and an increase in amplitude.

(6) *Effect on conditioning and avoidance responses.* On the assumption that psychoneurotic and psychotic conditions may be the result of faulty conditioning, numerous investigators have carried out studies relating to the effect of tranquilizers on conditioning and avoidance responses. In these experiments rats, cats, or monkeys were taught to escape to a pole or to another compartment at the sound of a buzzer in order to avoid an electric shock from the electrified floor of the cage given at a fixed interval after the buzzer sounded. Various refinements of this basic setup have recently been introduced. Administration of chlorpromazine, reserpine, or benactyzine blocked the conditioned response; the animals forgot what they had learned. At the sound of the bell the animals did not escape to the pole or to the other compartment as they would have done without drug treatment, but they stayed on the grating until they received the shock which, of course, induced an immediate escape reaction (Weiskrantz and Wilson, 1956; Smith *et al.*, 1956). Conditioned responses could also be blocked by morphine, alcohol, atropine, and scopolamine (Mikhelson *et al.*, 1954).

Meprobamate, on the other hand, did not affect the conditioned responses in any way. As long as the animal was physically able to move, it tried to escape as soon as the warning signal was given.

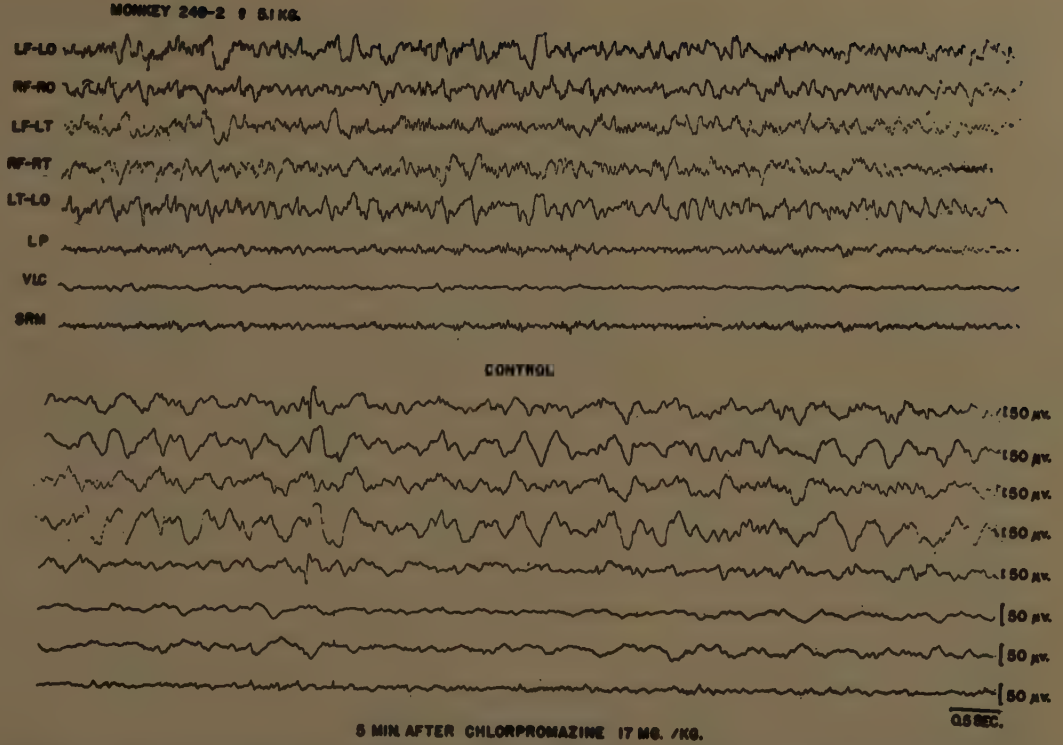


FIGURE 4. Electroencephalogram obtained from a rhesus monkey after intravenous administration of chlorpromazine 17 mg./kg. in divided doses within 2 hours. The record was taken 5 minutes after the last dose. LF-LO is the left frontal to left occipital; RF-RO, right frontal to right occipital; LF-LT, left frontal to left temporal; RF-RT, right frontal to right temporal; LT-LO, left temporal to left occipital; LP, nucleus lateralis posterior (thalamus); VLC, ventralis lateralis pars caudalis; and SRM, substantia reticularis mesencephali.

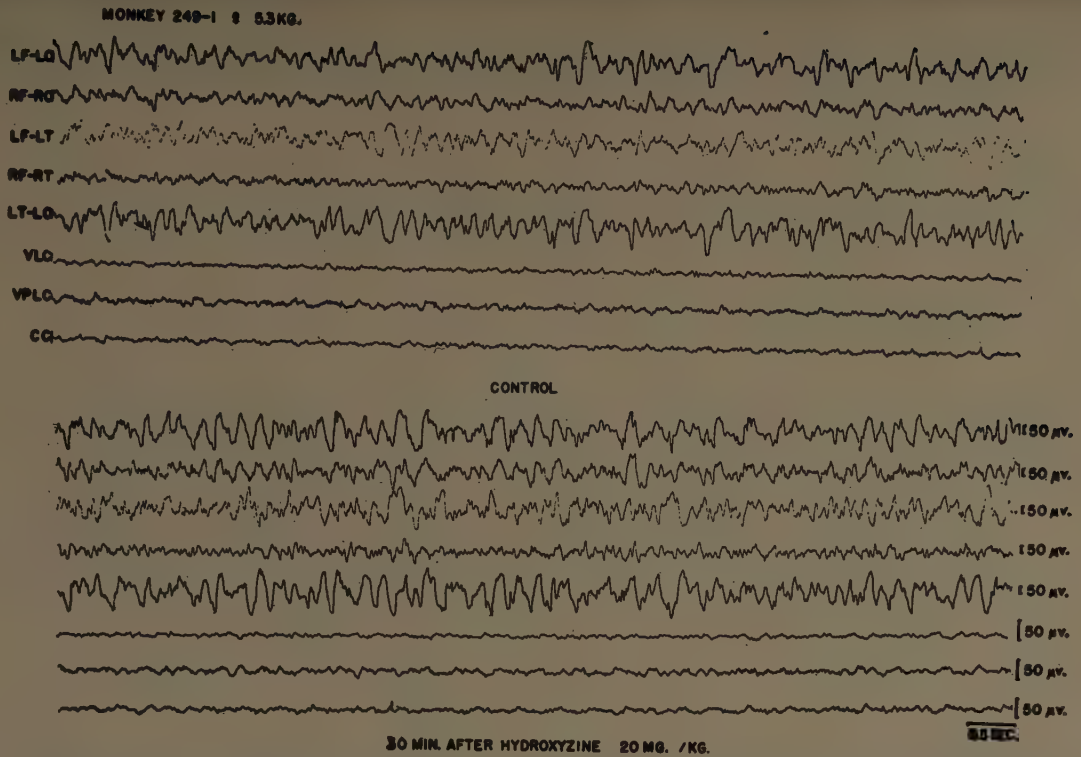


FIGURE 5. Electroencephalogram obtained from a rhesus monkey after the intravenous administration of hydroxyzine 20 mg./kg. LF-LO is the left frontal to left occipital; RF-RO, right frontal to right occipital; LF-LT, left frontal to left temporal; RF-RT, right frontal to right temporal; LT-LO, left temporal to left occipital; VLC, ventralis lateralis pars caudalis; VPLC, ventralis posterior lateralis pars caudalis; and CC, corpus callosum.

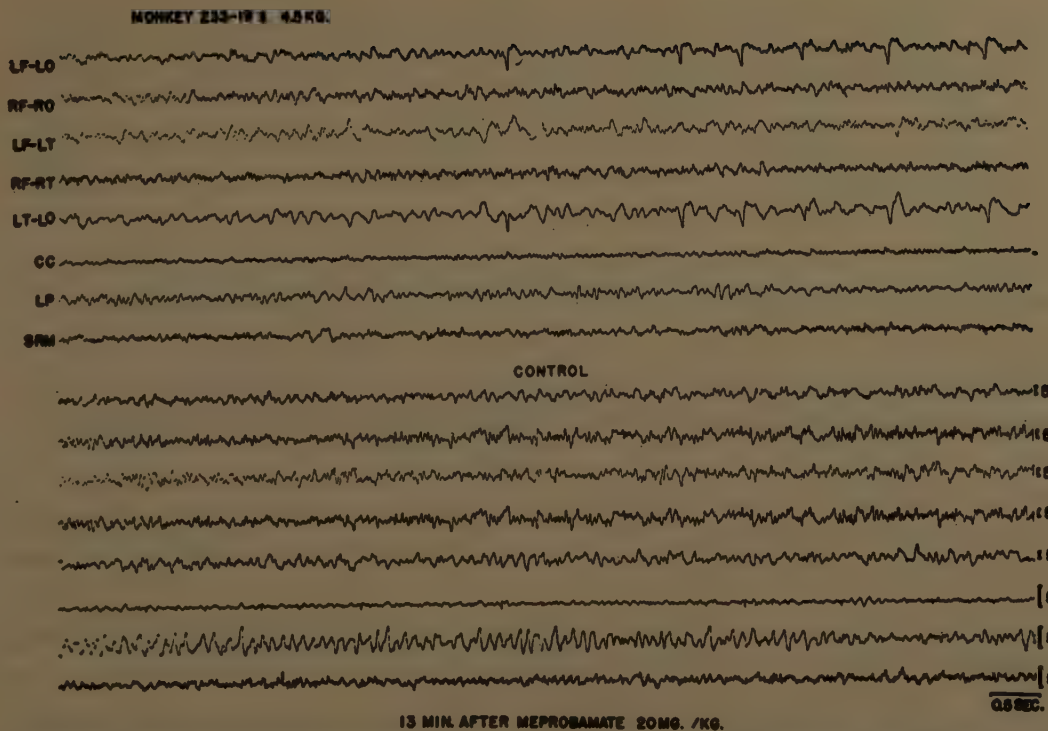


FIGURE 6. Electroencephalogram obtained from a rhesus monkey after the intravenous administration of meprobamate 20 mg./kg. LF-LO is the left frontal to left occipital; RF-RO, right frontal to right occipital; LF-LT, left frontal to left temporal; RF-RT, right frontal to right temporal; LT-LO, left temporal to left occipital; CC, corpus callosum; LP, nucleus lateralis posterior (thalamus); and SRM, substantia reticularis mesencephali.

Two Kinds of Tranquilizers

The comparison of the pharmacological properties of the tranquilizers permits the division of these substances into two pharmacologically distinct classes. The one group that could perhaps be called "autonomic suppressants," or tranquilizers in the narrower sense of the word, comprises the phenothiazines, reserpine, and the diphenylmethanes. The other group, called "central relaxants" is composed of meprobamate, mephenesin, and related compounds.

The autonomic suppressants have been so named because of their antagonism to such substances as acetylcholine, histamine, and serotonin, which regulate certain functions of the autonomic nervous system. These suppressants share many pharmacological properties with atropine, scopolamine, and the antihistaminics. Like atropine and scopolamine, these substances produce a sleep pattern in the electroencephalogram without necessarily producing sleep. Like atropine and scopolamine, they block avoidance and conditioned reflexes, perhaps by interfering in some way with memory, learning, and performance. Like antihistaminics, they prolong barbiturate anesthesia, perhaps by interfering with the enzyme acting on the barbiturate. They increase hyperexcitability experimentally produced by strychnine, and they lower the electroconvulsive threshold. In monkeys the autonomic suppressants reduce aggressiveness but, at the same time, they produce withdrawal, listlessness, anorexia, and catatonia. Normal persons taking these drugs often become apathetic and depressed, and lose initiative. They experience an "isolation from environment."

The central relaxants, on the other hand, do not affect the autonomic functions in any way. They prolong barbiturate anesthesia only in large doses and then only on an additive basis. Strychnine hyperexcitability is not increased but, on the contrary, can be counteracted by meprobamate. No nonspecific sleep pattern is produced in the electroencephalogram after small doses, but discreet changes in the thalamic structures are noted. Hostility is reduced in monkeys, while the animals still retain their appetite and their interest in their environment. Normal human beings not under tension ob-

TABLE 4

DIFFERENCES BETWEEN THE TWO GROUPS OF TRANQUILIZERS

Type of action	Autonomic suppressants	Central relaxants
Adrenolytic action	present	none
Anticholinergic action	present	none
Antihistaminic action	present	none
Strychnine toxicity	increased	decreased
Hexobarbital synergism	marked	slight
Conditioned reflexes	depressed	unaffected
EEG changes	generalized	localized
Convulsive threshold	decreased	increased
Multineuronal reflexes	unaffected	depressed
Afterdischarges	unaffected	decreased
Muscle spasm	unaffected	released

serve no somatic or mental changes after the administration of these drugs. The central relaxants have, however, a marked relaxant effect on spastic muscles and hyperexcitable multineuronal reflexes. Persons suffering from anxiety and tension also observe a diminution of their symptoms that at times may be dramatic.

Some of the differences between autonomic suppressants and central relaxants are summarized in TABLE 4. The two groups of tranquilizers differ from each other, not in the intensity of action, but in the kind of effect they exert, in their mode of action—as far as it is understood—and in their field of usefulness.

Mode of Action

Although the physical basis of mental disease has not yet been elucidated, it has been shown that many psychotics react abnormally to certain stimuli. These abnormal responses are apparently due to a low reactivity of the sympathetic centers in the hypothalamus, and they manifest themselves by lessened or different reactivity to cold, heat, Mecholyl, insulin, and electroshock. Procedures such as convulsive treatment that will stimulate the hypothalamic sympathetic centers are likely to produce remission in some of these patients.

It is possible that tranquilizers of the autonomic suppressant class are effective in the treatment of certain psychiatric conditions, not only because of their sedative action, but also becase of their stimulant effect on the sympathetic hypothalamic centers. These tranquilizers lower the convulsive threshold to electroshock seizures and to certain chemical convulsants (Jenney, 1954; Chen *et al.*, 1954; Berger *et al.*, 1956b) and increase the effects of strychnine, which is known to heighten the excitability of the posterior sympathetic hypothalamus (Gellhorn, 1956). According to this concept, the results of treatment obtained with this group of tranquilizers ought to be comparable to those obtained with insulin coma or electroshock, and indications that this may be the case have been reported (Gaitz *et al.*, 1955).

Many psychiatric patients, particularly psychoneurotics, also react in an abnormal manner to somatic stimuli. In these patients the low responsiveness of the hypothalamic sympathetic centers does not appear to be a factor; responses to stimuli tend to be exaggerated in intensity and duration (Malmo *et al.*, 1950). This increased reactivity may be due to defective inhibitory mechanisms in the reticular systems of the brainstem and the thalamus (Malmo, 1956). The effectiveness of the propanediols in psychoneuroses and anxiety states may be due to their selective blocking action on interneuronal circuits (Berger, 1949b) and to their ability to reduce exaggerated reflexes to the usual magnitude (Berger, 1947). Meprobamate, mephenesin, and other central relaxants will also reduce muscle tension that is often increased in emotional disturbances, and this effect may contribute to the clinical effectiveness of these agents. It appears that the central relaxants act in a manner that is entirely different from that of the autonomic suppressants. The relaxants appear to be of value primarily in the treatment of psychoneurotic conditions, while the autonomic suppressants are useful mostly in the treatment of psychoses.

In conclusion, we must ask whether we are justified in singling out the group

of substances discussed in this paper and calling them tranquilizers. This question cannot be answered with certainty at the present time, and the answer is unimportant. No pharmacological property common to all tranquilizers and unique to them has come to light. A definition of tranquilizers as agents that subdue excitement without producing undue sedation also appears untenable because, under suitable circumstances, barbiturates or scopolamine or other agents that have not been so labeled may act similarly. There is good evidence, however, that, at times, some of the tranquilizers do produce, in some patients, improvements that involve more than mere tranquilization. In any case, the introduction of tranquilizers has significantly advanced the development of psychiatry by contributing to the more general acceptance of the proposition that diseases of the mind are diseases of the brain and, as such, can be treated in a manner similar to that adopted for diseases of any other organ of the body.

Summary and Conclusions

According to their mode of action and their pharmacological properties, all tranquilizers can be divided into two groups: those that affect the autonomic nervous system and those that do not influence it. To the first group, called autonomic suppressants, belong the derivatives of phenothiazine, the *Rauwolfia* alkaloids, hydroxyzine, and benactyzine. The only important tranquilizer belonging to the class of agents that do not affect the autonomic nervous system (the central relaxants) is meprobamate. The two groups also differ from each other in a number of other important properties. Those that affect the autonomic nervous system (the autonomic suppressants) also block conditioned responses and lower the threshold to electroshock seizures and chemically induced seizures. They also potentiate the action of hypnotics and produce characteristic changes in the electroencephalogram that are related to those observed after the administration of atropine. In normal human beings they often produce a state characterized by insulation from the environment, and they may foster depression. These tranquilizers probably act in a manner not dissimilar to that of electroshock seizures or insulin coma, by stimulating the posterior hypothalamus. They act in a nonspecific manner on a variety of conditions by an action on the regulating centers.

Meprobamate differs in almost every respect from the tranquilizers of the autonomic-suppressant group. The drug does not affect conditioned responses and does not alter normal behavior. It increases the threshold for electrical or chemical convulsions. Meprobamate does not affect the hypothalamic regulating centers or normal responsiveness to stimuli, but it selectively reduces exaggerated responses. Since psychoneurotics tend to react to stress by exaggerated responses, it is expected that meprobamate will prove of particular value in the treatment of these conditions.

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Discussion of the Paper

K. Unna (*University of Illinois College of Medicine, Chicago, Ill.*): Berger has said little regarding the way the agents of the meprobamate-type compounds are acting and where they have their site of action. I think it should be pointed out that for the last six or eight years much work has been done in the investigation of the spinal cord as the site of action of mephenesin and of other agents of the phenothiazine type and of the peculiar effects that this entire group of drugs has on this site. When we compare meprobamate with mephenesin we find that large doses are necessary to produce depression of the multisynaptic pathways and that the depression obtained is of a smaller degree than that achieved with mephenesin.

Meprobamate is less effective than mephenesin as an internuncial depressant agent: We were very much surprised to find that, if we gave animals such as mice meprobamate intravenously, they did not demonstrate the relaxant effect at once, but endured a period of at least 15 min. during which the drug was apparently ineffective and during which the animal was highly excitable and particularly responsive to painful stimuli. The painful stimulus evoked hyperirritability, runs and wiggles, and other exaggerated reactions. I point this out because I believe there are conditions in which the drug does not produce relaxation but, on the contrary, a state of hyperexcitation, and in Berger's classification of these drugs I was not aware that he made any comparison with the barbiturates. I do believe this should be done in the classification of any such broad category as tranquilizers and, as Berger pointed out, one should not forget that barbiturates are also used for this purpose.

It would be helpful for a pharmacologist to have many more physiological experiments that would delineate the effect of meprobamate on certain of the preparations and would then differentiate those effects from those known for chlorpromazine and other investigated agents and compare them with the barbiturates. For instance, regarding the electroencephalogram, it does not suffice to say that treatment results in a slight diminution in frequency. This is relatively marked diminution in the scatter electroencephalogram and, with doses of meprobamate of 20 to 50 mg./kg. (which I think I can call small doses) there is a complete abolition of the awakening response, if the response is sought with leads suitable to the stimulus.

F. M. Berger: Meprobamate does have a somewhat weaker effect than mephenesin in the suppression of multineuronal reflexes. The effect of mephenesin, however, does not last more than 10 min., whereas with meprobamate the effect sets in slowly but lasts for several hours. This, I think, is a very important difference.

Concerning the barbiturates, I know they are widely used as tranquilizers. That is why I mentioned the comparison of chlorpromazine with barbiturates. I wanted to confine my remarks to agents that are now commonly described as tranquilizers, however, and barbiturates are not yet so described in the medical literature.

Question: I wonder whether the oral administration of these drugs will

affect the toxicity of strychnine or the action on acetylcholine and histamine, as distinguished from the other methods of injection; for example, the administration of one of these latter compounds orally prior to the administration of meprobamate, or perhaps the administration of both orally at the same time.

F. M. BERGER: It can be stated that strychnine is really used only as a tool, and that it will sensitize the posterior hypothalamic regulating centers. We have not investigated its effect when administered orally in other experimental setups.

QUESTION: I should like to know what intravenous dosage was used to produce the electroencephalographic changes, and what intravenous dose might be used to produce profound behavioral animal changes.

F. M. BERGER: The dose will vary from species to species and from animal to animal. In general, one would expect that the dose that produces changes in the electroencephalogram would also produce tranquilization.

QUESTION: Am I wrong in recalling that Harold Himwich, at a conference a year or so ago, took the position that, in the dosage employed in man, reserpine does not cause sleeping electroencephalographic patterns but, rather, concomitantly stimulates the mesodiencephalic learning system?

F. M. BERGER: I am sure that Himwich's observations as to arousal reactions are correct, but I wanted to confine myself to observations only on the gross electroencephalogram without stimulation. Also, reserpine is a difficult compound with which to work because it acts slowly; it requires as much as three hours to take full effect.

QUESTION: In classifying meprobamate with the propanediols, is it assumed that the meprobamate is being hydrolyzed before it has its activity? The other carbamates, of course, have been known for years to be sedative drugs, and meprobamate might act in the same way.

F. M. BERGER: The full metabolic fate of meprobamate is not yet known. The greater part of it is certainly conjugated with glucuronic acid. As Unna has pointed out, it takes 20 to 30 min. for the full pharmacological effects to set in, but there is no evidence that meprobamate would be hydrolyzed during this period.

As far as the question of potentiation of anticonvulsant is concerned, we have not investigated that, but we know that meprobamate, by itself, is an anticonvulsant.

EXPERIMENTAL STUDIES OF BEHAVIORAL EFFECTS OF MEPROBAMATE ON NORMAL SUBJECTS

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With the increasing use of meprobamate, it is important to know its effects on the behavior of relatively normal subjects, on persons who take the drug without discontinuing their usual activities. We need detailed information about the effects of the drug on those common but complex acts in which most people engage as part of their daily lives. One of these activities—potentially dangerous if not properly carried out—is driving an automobile. How does meprobamate affect the motor skills, the sensory processes, and the judgment necessary for safe driving? Does meprobamate in usual doses, alone or in combination with a martini or a drink of whiskey, make it likely that a driver will endanger his own life or the lives of others? The answers to these and related questions have become increasingly important in view of the rapid changes occurring in our modern world.

Although some information on these issues can be obtained from general observation and from subjective reports, our knowledge about the drug's effects will be much sounder if the data are obtained under standardized and controlled conditions. Our research, including studies of reaction time, driving skills, steadiness, and visual performance, was designed to accomplish this.

Drug Administration

Fifty adult subjects were tested on 5 successive days, on each of which they received one of the following doses: (1) a placebo (lactose, 1400 mg.); (2) meprobamate (800 mg.); (3) dextroamphetamine sulfate (15 mg.); (4) meprobamate (800 mg.) plus alcohol (2 oz. of 86-proof whiskey); and (5) a placebo (lactose, 1400 mg.) plus alcohol (2 oz. of 86-proof whiskey). The placebo, meprobamate, and dextroamphetamine sulfate were in capsules and were not identified to the subjects. There were 2 capsules of meprobamate in each treatment, 2 capsules for the placebo, and 1 for the dextroamphetamine sulfate. The whiskey was administered undiluted in a pony glass. Since the experimenters were, therefore, necessarily aware of some of the treatments given, the research design was not a "double blind," the procedure at present so highly regarded for evaluating drugs. Because we were using objective behavioral measures, however, the blind method did not seem so essential as when effects of drugs on patients are to be rated or evaluated clinically. It seems unlikely that the information unavoidably revealed to the experimenters could have affected the scores on any of our procedures. Perhaps an ultimate objective quantification of such measures of change may eliminate the need for elaborate double-blind controls.

Testing Procedures

All the subjects were tested in small rooms in the Ann Arbor Veterans Administration Hospital. Testing was done on consecutive working days, omitting week ends, and each subject was tested at approximately the same hour each day. On the first day of testing the experimenter explained to the subject that the purpose of the experiment was to learn the effects of certain drugs on driving, and that the drugs administered would have no serious effects. It is likely that most of the paid subjects knew through "the grapevine" that meprobamate and alcohol were two of the drugs to be used, but they were not so informed by the experimenters. In order to permit the most efficient use of time, subjects were seen in pairs. While one was operating the auto trainer in one room with one experimenter, the other was being given the remaining tests in another room by a second experimenter. The tasks were then switched.

Upon entering the waiting room the subjects were given one of the drugs or placebos; a 30-minute waiting period was allowed for it to take effect. The order of presentation of the drugs over the 5-day period varied from subject to subject in such a way that each treatment occurred equally often at each stage of practice, and each treatment followed every other treatment with equal frequency. Each day the subject received a different treatment, so that at the end of the 5-day testing period he had received them all. During the waiting period on the first day the subjects were interviewed for background and personal information and were given a 15-minute practice session on the driving task. Half received the interview first, and half received the driving practice first.

Subjects

Of the 50 subjects, 36 were men and 14 were women. The range in age was from 21 to 50, 30 of the subjects being between 21 and 29. Twenty-nine were college students, 9 were patients with medical (not neuropsychiatric) illnesses in a Veterans Administration hospital, 5 were patients in a neurosis center, and 7 were Veterans Administration employees. Most of these persons were normal, in the sense that they did not suffer from obvious personality difficulties or mental illnesses, and none was psychotic. Thirty-seven replied "no" to the question, "Have you or has any member of your family been bothered by fits, faints, or nervousness?" Of the remainder, 8 gave a personal history, 3 a family history, and 2 both a personal and a family history of such symptoms. It appeared to us that this probably was a reasonably representative sample in terms of the mental status of the types of persons at present receiving meprobamate.

Of those subjects who were hospital patients, 9 had been hospitalized less than 1 month, 1 for 1 month, 1 for 2 months, 2 for from 3 to 5 months, and 1 for between 6 months and a year.

All subjects were volunteers. The student subjects were paid, while the others were not.

Because of the relationships of body weight to drug effects, the subjects' weights were taken. Eleven weighed between 90 and 124 lb., 11 between 125

and 139, 4 between 140 and 154, 9 between 155 and 169, and 9 between 170 and 184. The remaining 6 weighed more than 185 lb.

Thirty-four of the subjects were accustomed to driving daily, 7 drove at least weekly, and only 9 drove seldom or not at all.

Forty of the subjects reported that they had never taken tranquilizing drugs; the other 10 had taken them only infrequently. Thirteen said they were moderate drinkers, 31 reported they were light drinkers, and 6 said they did not drink alcohol at all. None admitted being a heavy drinker or having a history of alcoholism.

Apparatus and Results

For the driving tests, the American Automobile Association's "Auto Trainer" was used (FIGURE 1). This apparatus consists of 2 parts: the first includes all the controls of a conventional-shift automobile—starter button, speedometer, steering wheel, gear-shift lever, ignition key, and accelerator, brake, and clutch pedals; the second part is a treadmill-like belt about 10 feet long, which extends from the front of the control unit. The belt, painted to resemble a tortuous roadway, revolves when the controls are in gear, the speed being controlled by the accelerator. In our experiment, however, the apparatus was modified so that the speed could be set by the experimenter's controls at a constant fast

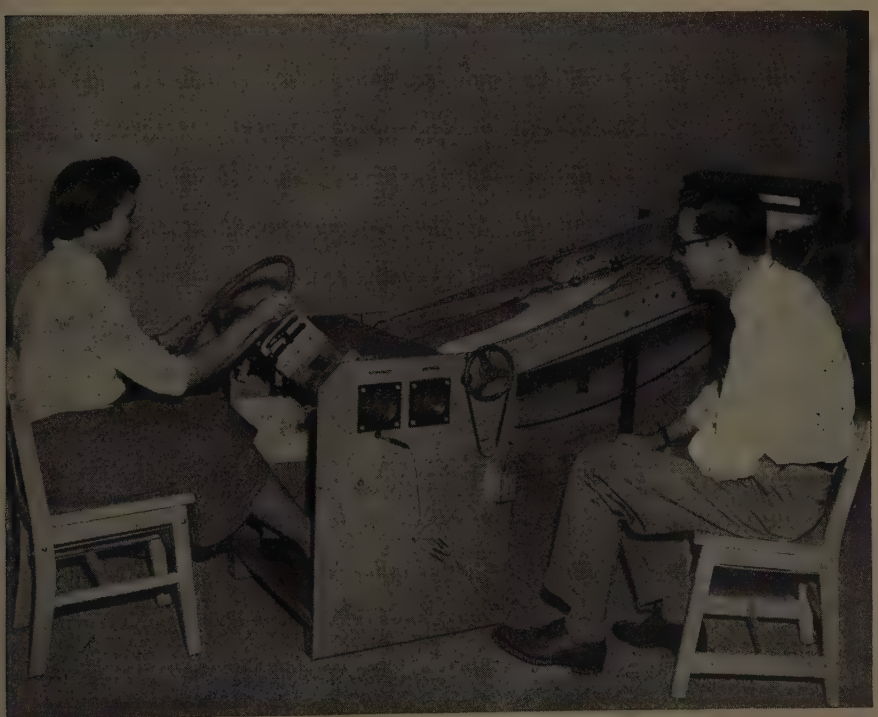

FIGURE 1. American Automobile Association's Auto Trainer, used for the driving test.

rate (equivalent to approximately 20 mph) or a slow rate (approximately 10 mph).

A small model car, the steering mechanism of which is controlled by the steering wheel of the control unit, rests on the belt, its wheels turning as the belt revolves, and the speed of the belt determines its apparent speed. The task of the subject is to steer the car so that it remains in the center of the roadway painted on the belt. A red and a green light are situated at the far end of the belt unit. When the green light is on, the driver is to proceed; when the red light appears, he is to stop the car as rapidly as possible by depressing the brake.

An accuracy counter, a reaction timer, a trial timer, and speed controls face the experimenter at the side of the control unit, out of sight of the subject. A foot switch with which the experimenter can turn on the red light is also connected to the side of the unit. Large staples are embedded in the "roadway" every 3 inches. If the car is kept in the center of the roadway, it makes contact with the staples, completing an electrical circuit and advancing the accuracy counter 1 unit. The reaction timer measures in hundredths of a second the time elapsed between the appearance of the red light and the brake-pressing response.

The subjects were given trials as follows: 20 revolutions of the belt at a fixed slow speed; 20 at a fixed fast speed; and 20 at a speed controlled by the subject. Six reaction-time determinations were interspersed irregularly through each of the 3 trials.

On the driving test, scores were obtained for accuracy at the fixed low speed, at the fixed high speed, and at the variable speed controlled by the subject. The unit of measurement was the number of staples over which the car passed. It will be remembered that the staples were embedded in the center of the roadway so that the subject had to keep the car in the middle of the road to activate the accuracy counter. In addition, a time score was obtained, indicating the time required for each trial when the subject was controlling his own speed. During this phase of the test the subject was asked to drive as rapidly and accurately as he could. A derived score was also figured—the ratio of the difference between the accuracy score at low fixed speed and the accuracy score at subject-controlled speed, divided by the time score. This speed-accuracy ratio, which indicated the degree to which speed was sacrificed for accuracy, or vice versa, may be interpreted as a measure of judgment. Scores on the driving-test measures and on all other tests under the various drug conditions, as compared with the placebo condition, are presented in TABLE 1.

Reaction times for the brake-pressing response were taken while the car was being driven at low fixed speed, at fast fixed speed, and at variable speed. As can be seen in TABLE 1, none of the drug treatments produced a significant change on the speed of reaction, nor on any of the other driving-test scores*.

* The lack of significant difference in braking time under meprobamate and under placebo is consistent with our earlier study of visual reaction time in 20 subjects under laboratory conditions. The reaction times of each subject were measured in a session twice daily for 3 successive days. Each session consisted of 10 separate reaction-time measurements after 3 practices. No drug was given the first and third days, but the trials on the second day were conducted 6 and 12 hours after the subjects had taken 800 mg. of meprobamate. The findings indicated that meprobamate does not lengthen visual reaction time so measured.

TABLE 1

MEAN DIFFERENCES BETWEEN SCORES UNDER EACH OF FOUR DRUG CONDITIONS AND UNDER PLACEBO

Tests	Differences between scores in standard deviation of placebo action			
	Meprobamate	Meprobamate and alcohol	Placebo and alcohol	Dextro-amphetamine sulfate
Driving tests				
Accuracy				
Fixed low speed	+0.16	+0.04	−0.05	−0.07
Fixed high speed	+0.06	+0.04	+0.06	+0.01
Variable speed	+0.04	−0.08	+0.07	+0.02
Time				
Variable speed	−0.16	−0.08	−0.10	−0.08
Judgment	+0.05	+0.07	−0.05	−0.06
Reaction time				
Fixed low speed	−0.15	−0.19	−0.21	+0.17
Fixed high speed	−0.04	−0.12	+0.04	+0.20
Variable speed	−0.10	−0.27	−0.14	+0.06
Palmar perspiration test	−0.35*	+0.05	−0.08	−0.22
Steadiness test				
Largest hole	+0.06	−0.09	−0.26	−0.19
Next to largest hole	+0.03	−0.09	−0.20	−0.09
Medium hole	+0.04	−0.14	−0.30*	−0.01
Next to smallest hole	−0.16	−0.13	−0.16	−0.07
Smallest hole	+0.04	+0.03	−0.01	+0.17
Visual tests				
Depth perception				
Distant	+0.07	+0.03	+0.07	+0.03
Acuity				
Distant	−0.05	−0.09	0.0	−0.05
Near	−0.09	−0.09	−0.09	+0.05
Vertical phoria				
Distant	+0.08	0.0	−0.08	0.0
Near	+0.15	0.0	−0.08	+0.08
Lateral phoria				
Distant	0.0	−0.06	−0.06	−0.06
Near	−0.07	0.0	+0.04	−0.07

Symbols: + indicates that the drug effect was more favorable than the placebo effect; − indicates that the placebo effect was more favorable than the drug effect.

* The probability is less than one in a hundred that this result could have occurred by chance.

In order to secure a measure of autonomic response, as an index of anxiety, the perspiration during the driving test was recorded.

The technique used is an adaptation of the one used by O. H. Mowrer. The subject's thumb is swabbed with a solution of ferric chloride (13 gm. of anhydrous ferric chloride in 400 cu. cm. of chemically pure acetone, with 3 drops of hydrochloric acid added to stabilize the solution). A small square of paper, soaked in a 5 per cent aqueous solution of tannic acid and allowed to dry, is placed on the thumb and held firmly by a small foam-rubber pad taped to the subject's thumb. The pressure with which the pad is taped to the thumb is roughly controlled by attempting to equalize the amount of compression of the pad for every administration. The pad is worn throughout the driving test.

As the subject perspires, the ferric chloride dissolves and makes a stain on the paper. The darkness of the stain is proportional to the amount of sweating.

A score is obtained by placing the ferric chloride paper over the half-inch aperture in a transmission-type photometer and reading the percentage of light transmission of the darkest area. One hundred per cent transmission is set at the amount of light transmitted by the nonstained part of the paper, and the score is expressed in percentage of this value.

The temperature and relative humidity of the testing room were also recorded during all the testing sessions, so that these variables could be controlled statistically in evaluating the measure of perspiration.

The results of the perspiration measure were clear-cut. Perspiration was significantly greater under meprobamate, as compared with the placebo. Dextroamphetamine sulfate and alcohol did not produce any definite effect. The results with meprobamate were exactly contrary to expectation, so we double checked to determine that there had been no error in recording or computing the scores.

Intercorrelations between palmar sweating and room humidity and temperature were so low under meprobamate and under placebo that correlated changes in these variables could not explain the difference. Moreover, our data analysis showed a similar effect in males and females, so the over-all results cannot be explained by any differential, such as degree of vasomotor stability, between the sexes. Males sweated more than females under all conditions. It is unclear in the literature and to us whether the perspiration test is, as usually sug-

FIGURE 2. Apparatus for the Whipple Steadiness Test.

gested, a measure of anxiety, or whether it may be related more to muscular exertion or some other function.

The steadiness test used is an adaptation of the Whipple Steadiness Test (FIGURE 2). The test panel contains a series of holes decreasing in size from $\frac{7}{16}$ in. to $\frac{3}{16}$ in. The subject is asked to insert a round metal stylus $\frac{1}{8}$ in. in diameter into each of the holes and to hold it there for 15 sec. without letting it touch the sides of the hole. The apparatus is wired so that a timer is activated whenever the stylus touches the sides of the hole during the 15-sec. test period.

Scores were obtained for 3 trials on each of the 5 holes, representing the total amount of time that the stylus touched the rim of the hole. The scores were weighted to compensate for the varying difficulties of task for each hole, in making direct comparisons and to facilitate combination of the scores from the different-sized holes. For weighting, the scores for the $\frac{7}{16}$-in. hole were multiplied by 10; the $\frac{6}{16}$-in. hole, by 4; the $\frac{5}{16}$-in. hole, by 1; the $\frac{4}{16}$-in. hole, by $\frac{1}{4}$; and the $\frac{3}{16}$-in. hole, by $\frac{1}{10}$.

With placebo and alcohol there was a significant impairment of steadiness for the medium-size hole, but not with meprobamate or dextroamphetamine sulfate. There was a similar impairment (nearly to the level of significance) for the other 3 of the 4 largest holes. There was a suggestion that meprobamate tends to counteract alcohol.

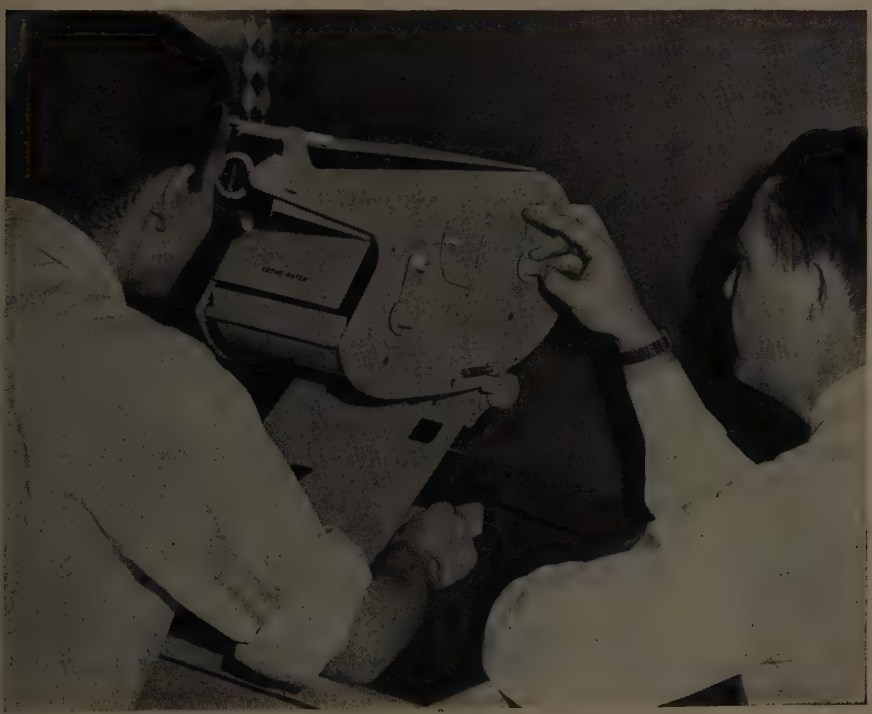

FIGURE 3. Bausch and Lomb master-model Ortho-rater.

For the visual tests we employed the master-model Ortho-rater (FIGURE 3) constructed by the Bausch and Lomb Optical Company, Rochester, N. Y. This device is designed to present slides for testing various visual functions, with distance and illumination controlled. It consists of 2 octagonal slide-holding drums set inside a boxlike apparatus. A binocular eyepiece is located at one end of the box. One of the drums is much closer to the eyepiece than the other and is used for testing near vision; the farther drum is used for testing distant vision. The test slides are fastened to the drum and are easily changed by rotating the drum with an external handle. Standard Ortho-rater testing procedures were used for 7 visual tests.

Acuity was determined for both far and near vision; depth perception scores were determined for distant vision only. Vertical and lateral phorias for both near and far vision were also measured. Phoria scores indicate the relative posture or muscular balance of the eyes in relation to each other under conditions of controlled accommodation. A perfect vertical phoria score indicates that the horizontal midline in both the right and left visual fields is in the same axis. A perfect lateral phoria score indicates the same for the vertical midline. In TABLE 1 the plus scores would indicate exophoria; minus scores would indicate esophoria.

The results of the visual tests yielded no significant differences between the drugs and the placebo.

Summary of Meprobamate Effects

In the analysis of results, using the critical ratio of correlated measures, we compared all possible pairs of treatments on all test scores, as well as temperature and humidity readings during the perspiration test—a total of 230 critical ratios and correlation coefficients. The same statistical analyses were also done separately for the males alone and for the females alone. No clear sex differences in the effects of meprobamate were demonstrated; the results, therefore, are reported for the total group of subjects.

The intercorrelations between scores on all 23 test variables were also obtained for the placebo condition and for the meprobamate condition. The several measures of accuracy, of reaction time, and of steadiness were highly intercorrelated, suggesting that each set of these alternate measures validly samples a single domain.

The correlation coefficients between the scores on any one test on different days, that is, under different drug treatments, ran between 0.45 and 0.90, with a median of 0.68. This indicates a satisfactory reliability for the different measures.

In TABLE 1 the column headed "Meprobamate" shows the mean differences between the scores obtained under meprobamate and placebo conditions on the driving tests, the perspiration test, and the steadiness and visual tests. The plus scores represent differences in which the performance is more favorable under meprobamate. Deciding what direction of effect is favorable on any test naturally involves a value judgment but, in most cases, there could be

TABLE 2

MEAN DIFFERENCES BETWEEN SCORES UNDER MEPROBAMATE AND ALCOHOL, AND UNDER PLACEBO AND ALCOHOL

Differences Between Scores in Standard Deviation of Placebo and Alcohol Action

Driving tests	
Accuracy	
Fixed low speed	+0.08
Fixed high speed	−0.02
Variable speed	−0.14
Time	
Variable speed	+0.01
Judgment	+0.09
Reaction time	
Fixed low speed	+0.01
Fixed high speed	−0.15
Variable speed	−0.12
Palmar perspiration test	+0.12
Steadiness test	
Largest hole	+0.15
Next to largest hole	+0.08
Medium hole	+0.12
Next to smallest hole	+0.01
Smallest hole	+0.03
Visual tests	
Depth perception	−0.03
Acuity	
Distant	−0.10
Near	0.0
Vertical phoria	
Distant	+0.10
Near	+0.07
Lateral phoria	0.0
Distant	0.0
Near	−0.03

Symbols: + indicates that the meprobamate and alcohol effect was more favorable than the placebo and alcohol effect; − indicates that the placebo and alcohol effect was more favorable than the meprobamate and alcohol effect.

little argument. The only significant difference here is the greater amount of perspiration with meprobamate. As we have noted, this result is unexpected, and its interpretation is not clear.

What are the effects of alcohol as contrasted with those of meprobamate and alcohol together? In TABLE 1 the columns headed "Meprobamate and alcohol" and "Placebo and alcohol" show the effects of these drugs as compared with the placebo on all of the tests. The only statistical significance revealed is the effect of alcohol on the measure of steadiness. Perhaps the absence of other clear-cut effects of alcohol on driving and vision can be attributed to the relatively small dosage of less than 1 oz. of alcohol. Comparing the results for the combined meprobamate and alcohol offers no evidence that the combination has any more unfavorable effects than alcohol alone.

A direct comparison of the performances on the same tests under alcohol and under alcohol plus meprobamate yields the findings shown in TABLE 2. The plus scores indicate more favorable performance under combined alcohol and meprobamate as compared with alcohol alone. None of the differences is statistically significant.

Examination Performance and Anxiety

Another research study provides more general evidence for the absence of deleterious effects of meprobamate on normal functioning. This experiment was carried out in collaboration with Wilbert McKeachie of the Department of Psychology at the University of Michigan. In connection with a regular mid-term examination in a college psychology course, a class of 276 students,

after being assured it would have no serious effects, agreed to take a pill of unstated composition 1 hour before the examination*. Selected at random, 138 of the students received 400 mg. of meprobamate, and 138 received a placebo (5 gm. of acetyl salicylic acid). Performance on the examination was not impaired for those who received meprobamate; indeed, it was slightly better, as might be expected, since it is obvious that anxiety and apprehension interfere with efficiency on examinations. Support for this interpretation comes also from the answers to 5 questions at the end of the examination, asking about worry and stress during the period. The students who received meprobamate reported somewhat less anxiety than the others, but the difference was not clearly significant.

An unexpected finding in these results was that meprobamate had a greater effect on females than on males, both in improving examination scores and in reducing anxiety. In the research on driving, we also found that dextroamphetamine sulfate, and perhaps other drugs, produced greater performance effects on females than on males. Since body weight was not taken into account in the dosage, the interpretation of these findings is not clear. However, sex differences in drug action are well known, as, for example, in the hypnotic effects of barbiturates.

Summary

The primary finding of these studies is that meprobamate alone, even in double the usual dosage, produces no behavioral toxicity in our subjects as measured by our tests of driving, steadiness, and vision. Meprobamate significantly increases sweating, an unexpected and unexplained finding.

Our study also indicates that, while alcohol definitely impairs performance on some tests, combining meprobamate with the alcohol does not significantly add to this unfavorable effect on any test. Our data give no grounds for preventing persons under the usual dosages of meprobamate from driving automobiles, or even from driving under meprobamate after drinking alcohol in amounts that would not ordinarily affect driving ability.

Acknowledgments

The authors thank Sidney Perloe and Richard Metz, who administered the tests and assisted throughout the research, and Lillian Kelly, who did much of the data analysis. We also express our gratitude to the United States Veterans Administration Hospital in Ann Arbor for providing space and many of the subjects for this study, and to the Veterans Readjustment Center for providing subjects.

Discussion of the Paper

QUESTION: I should like to put a faint note of caution on the all-sweeping summary that the doses of meprobamate do not interfere with judgment or mechanical skill, or that doses of meprobamate plus alcohol are not in any

* We recognize, of course, that such assurances could have a suggestion effect on the outcome, but they were obviously necessary in order to obtain co-operation of the subjects.

way synergistic. I feel that the enthusiasm for the experiment, while it is excellent for the first series of tests, certainly does not take into consideration what Berger has already emphasized, namely, that with meprobamate there is a considerable latent period before action takes place. Many people who take meprobamate do so, not once a day, but three, four, or more times a day for several days. At the end of such a period of dosage the residual effects from many partially destroyed doses of meprobamate could be considerably greater than even the one double dose. I cannot question the results as presented, but I do advise caution in their application.

D. G. MARQUIS: Certainly we have no desire to generalize beyond the reasonable limits represented by the particular test data. The latent period of meprobamate is no more than 30 min., and we used a 30-min. waiting period. The tests extended over an hour following this waiting period. Since the usual dosage is 1 pill every 4 hours, we were given no reason to believe that there would be a cumulative effect any greater than the effect of 2 pills taken simultaneously.

QUESTION: I wonder if Marquis has any comments to make regarding the distribution within the group that averaged out as nonspecific. Were there any patterns that suggested that some people behaved differently than others under these conditions?

D. G. MARQUIS: Certainly there were individual differences, but there is no way to evaluate their significance except by a system of subgrouping of the individuals. While we did find differences in magnitudes, such as the fact that women do not sweat as much as men, the drug effects were always in the same direction.

SOME EFFECTS OF MEPROBAMATE ON CONDITIONED FEAR AND EMOTIONAL BEHAVIOR*

By Howard F. Hunt
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For a number of years we have been investigating conditioned fear, or "anxiety,"[1, 2] and other emotional behavior in rats. Previous reports have described the general outlines of the program and the specific results obtained to date.[2-6] More recently, this enterprise has been extended to the study of the effects of selected drugs.[6]

The basic conditioning paradigm is simplicity itself. An ordinarily neutral stimulus (usually a clicking noise), the conditioned stimulus (CS), is presented for several minutes and is then terminated approximately simultaneously with the presentation of one or two painful shocks to the feet, delivered through the grill floor of the apparatus. After a few such pairings (often after only one) the CS acquires the power to suppress, partially or wholly, intercurrent ongoing behavior. The behavior so suppressed may be a previously established activity such as lever pressing for a water reward (in the lever-pressing apparatus) or exploratory behavior (in the grill box). The conditioned rats normally show a tense crouching or "freezing" reaction during the presentation of the CS, and usually defecate as well. My associates and I have called this behavior a conditioned emotional response (CER)—"conditioned" because a neutral stimulus acquires the power to evoke it, "emotional" because it includes defecation as a part of the pattern, and "response" because the indicator is an objectively identifiable change in behavior.[2, 3]

The superimposition of conditioned fear on some regularly recurring behavior such as lever pressing makes it possible, by experiment, to distinguish between loss of the conditioning as a function of general deterioration or debility resulting from experimental treatments and loss of conditioning as a result of the more specific action of the experimental variable on some aspect of the conditioning as such. Further, the operant upon which the fear is superimposed can be varied in strength by manipulation of the parameters that govern it independently of the parameters that govern the strength of the conditioned fear. This allows adjustment of the sensitivity of the tests and permits a reasonable approach to quantifying the strength of the conditioned fear in terms of the magnitude and duration of the suppression of lever pressing. In the grill box the exploratory movement suppressed by CER is considerably less amenable to independent control, limiting control over the sensitivity of the tests in that apparatus.[5]

Previous experimental and clinical reports have indicated that meprobamate not only acts as a muscle relaxant of longer duration than mephenesin, but also

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that it has taming effects on some animals and tranquilizing effects on human psychiatric patients.[7, 8] The present paper is concerned primarily with the effects of meprobamate on the CER. The drug was of particular interest in our program because it appeared to produce its effects on emotional behavior by influencing functions other than autonomic actions of this sort. The CER in rats should not be equated directly with "anxiety" as it appears in human beings, but the conditioning seems closely analogous to the kind of learning that comprises the fundamental units out of which more complex human maladjustment is elaborated.

In preliminary trials with trained rats, carried out by John Harvey and myself, meprobamate in doses of 80, 160, and even 240 mg./kg., administered intramuscularly, did not consistently or significantly interfere with lever pressing for an aperiodic water reward (available on the average of once per minute on an automatically controlled variable-interval schedule[2]). Animals given regular 12-minute runs in the lever apparatus under the drug treatment made about as many lever responses as they made when run under saline, and they did not consistently make either fewer or more lever responses than control animals run under saline.

All animals received a total of 7 CER conditioning trials during the lever-pressing runs. Those conditioned under meprobamate acquired the CER about as rapidly and strongly as those conditioned under saline. As in the earlier part of the experiment, all animals were on a 23½-hour water-deprivation schedule, and the drug or placebo was injected 2 hours before each run. Further, the different dosages produced no consistent differences in the rate of conditioning or the symptomatic strength of the emotional response.

So few animals were used in these experiments (6 experimental and 6 control animals) that we repeated the experiment with modifications to provide for a better initial survey. First, 20 naïve male albino rats 60 to 80 days of age received standard lever-pressing training, first for the regular and then for the standard aperiodic water reward. All were deprived of water for 23½ hours prior to each of the daily 9-min. runs. After lever pressing for aperiodic reward had stabilized, the rats were divided randomly into 2 groups of 10 each. The experimental animals received injections of meprobamate (80 mg./kg.), and the control animals received equivalent saline placebo 60 to 90 min. prior to the lever-pressing run on each of 4 consecutive test days. On the first 3 test days the injections were subcutaneous; on the 4th day, because the experimental animals had developed a severe dermatitis, the injections were intramuscular.

These tests confirmed and extended the earlier findings. Meprobamate did not interfere with the output of lever pressing. Indeed, most of the differences between the means for experimental and control groups appeared to be in the opposite direction, with the experimental animals showing somewhat higher output on two test days during which unseasonably warm weather depressed quite uniformly the output of the control group. The warm weather had a less severe and much less consistent effect on the output of the meprobamate group. This is reflected in the significant differences in variability between the groups on the 2nd and 4th test days ($P < 0.01$ and < 0.001,

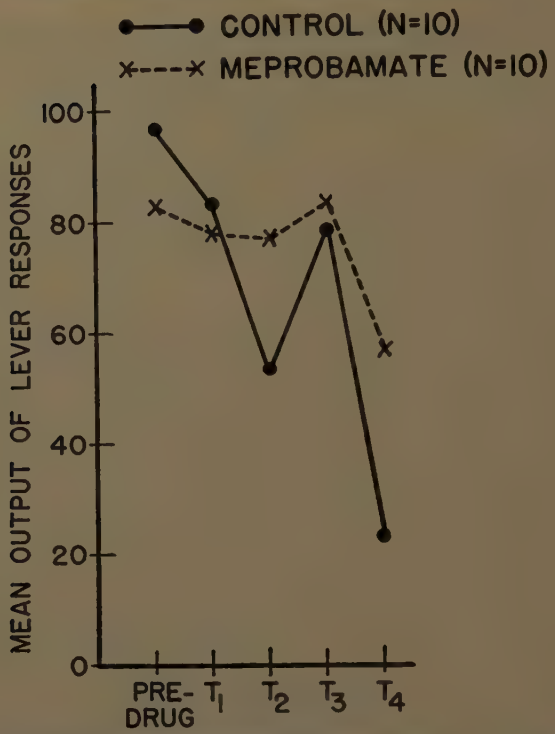

FIGURE 1. Effect of meprobamate on the mean output of lever responses.

respectively). FIGURE 1 shows the group means for the last predrug or preplacebo run and for the test days. The differences in mean output for the 2nd and 4th days reflect the fact that a number of the meprobamate rats on each of these days failed to show any substantial decline in output in reaction to the somewhat elevated temperatures prevailing in the laboratory at those times, while the output of the control animals dropped quite consistently.

At this point the lever apparatus tests were discontinued and CER conditioning was carried out in the grill box, where highly probable daily fluctuations in temperature would complicate the interpretation of the data to a substantially lesser degree.

All animals had a week of rest without medication and with free access to food and water in the home cages. Then the 23½-hour water-deprivation schedule was reinstituted; the experimental animals again received daily intramuscular injections of meprobamate (80 mg./kg.), and the control animals were given equivalent saline. On the 3rd day of deprivation and medication all animals began CER conditioning in the grill box in accordance with standard procedure.[3] Each run in the apparatus followed the injections by 60 to 90 min.

All rats received a total of 9 CER conditioning trials, each consisting of a 3-min. presentation of the CS terminated by 2 momentary, 1.0 mAmp. shocks

to the feet during the second 3-min. segment of the daily 9-min. runs in the apparatus. After the second conditioning trial all animals received one adaptation run in the apparatus (no CS or shock presented). Between the 8th and 9th conditioning trials all received 2 days of rest in the home cages. The water deprivation and injections continued throughout the conditioning period.

After this conditioning and following 5 days of rest on drug or placebo, but with free access to food and water, all animals received a total of 7 test-extinction trials, 1 per day, under the appropriate condition of medication. In each trial the rat received a 3-min. presentation of the CS, but no shocks, at the usual time during a run in the apparatus. After this the injections were stopped and the animals had 6 days of rest on full food and water. Finally, all animals were returned to the 23½-hour water-deprivation schedule and were given, without medication, 4 more test-extinction trials in the grill box.

Because we expected that whatever effects meprobamate had on CER conditioning would be subtle, we adopted an arbitrary scoring procedure with the hope of making the grill-box situation more discriminating. Each animal received a point for each 30-sec. segment of the 9-min. run during which he moved*, and a score of 0 for that segment if he remained motionless. The total possible score for the 3 min. prior to presentation of the CS, for the 3 min. of the CS, or for the 3 min. after termination of the CS and the administration of the shocks would be 6 if the animal moved at least once during each 30 sec., with a total possible score of 18 for the entire run.

As indicated earlier, the CER appears as a suppression of output; in the grill box it appears as a reduction or cessation of exploratory behavior and "random" movement. Thus, if a rat remained absolutely motionless during presentation of the CS as a result of CER conditioning, his score for that segment would be 0. If his CER had become very strong and was generalized to the apparatus, he would move very little even though the CS was absent, as would be the case during the 3 min. prior to presentation of the CS in a conditioning run or during the second 3-min. segment of an adaptation run. Further, this scoring method can show the suppressant effect of the CS on movement by way of a modification of the inflection ratio, a monotonic but nonlinear score used to describe the CER as it appears in the lever apparatus.[5] The ratio is $\frac{B-A}{A}$, where B is the movement score during the 3-min. presentation of the CS, and A is the movement score for the preceding 3-min. segment of the run. The ratio expresses, in decimal form, the percentage of reduction in activity during the CS as compared with the preceding segment: it increases in the negative direction as the CER becomes stronger, and shifts toward 0 as the CER becomes weaker.

* The decision as to whether an animal "moved" during any given 30 second period was arbitrarily arrived at as follows: The animal was observed continuously during each run. Every 5 seconds a mark was made if the animal had moved *at all* during the preceding 5 seconds. If an animal moved *at all* in more than 3 of these 5 second intervals, he received a point for that 30 second period. If he moved *at all* in 3 or fewer of the 5 second intervals, he received a score of 0 for the 30 second segment.

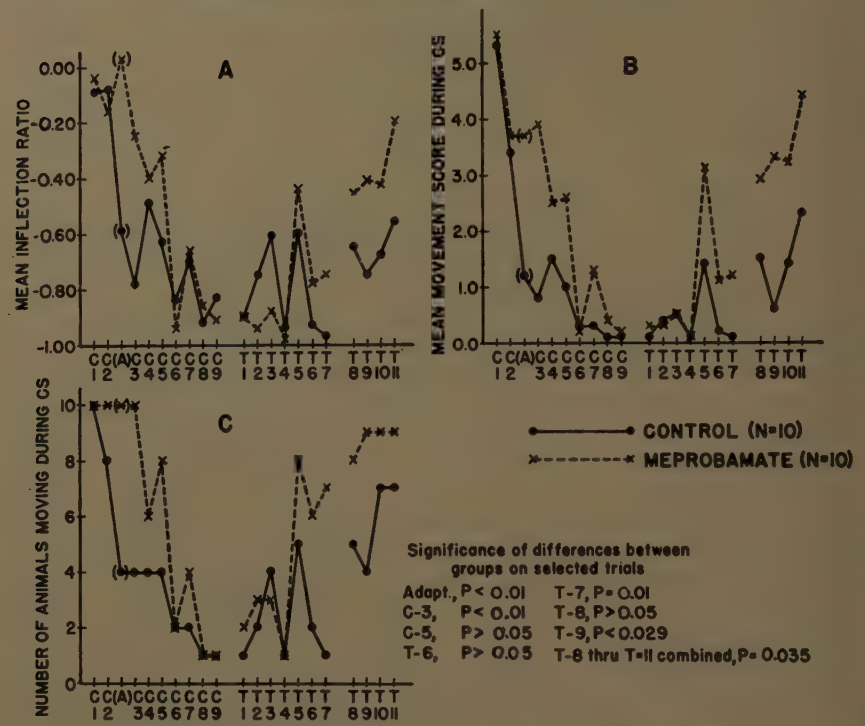

FIGURE 2. Effect of meprobamate on a CER established in the grill box.

FIGURE 2 shows the effect of meprobamate on CER conditioning in the grill box in terms of movement scores in the 9 conditioning and 11 test-extinction trials. The adaptation trial is included in brackets, after C2, to show the difference between the groups in the generalization of the CER at this early stage in conditioning. Panel A shows the mean inflection ratios for the groups, panel B the mean movement score during the presentations of the CS, and panel C the number of rats that moved during the CS (or during the comparable segment of the adaptation run). Of course, these curves are somewhat more irregular than equivalent data from CER conditioning in the lever apparatus. There the behavior suppressed by the CER can be controlled more precisely than exploratory movement, so that the quantitative expression of CER conditioning can be graphed more smoothly.

All animals, both experimental and control, acquired a strong CER by the 9th conditioning trial, and all retained it over the 5-day rest period, as indicated by crouching or "freezing" during presentation of the CS in the 9th conditioning trial (C9) and the first test trial (T1). The ratios and scores in FIGURE 2 reflect this observation. The meprobamate and saline groups were practically identical in performance during the last few conditioning trials and early in extinction (the differences in panel A for trials T2 and T3 do not even approach statistical significance). This indicates that meprobamate does not

block the expression of the CER in any degree comparable to the decisive way that Brady has found reserpine to block it.[9] Nor does meprobamate interfere with extinction of the CER, as our data suggest that chlorpromazine does.[6] This does not mean, however, that the drug has no effect on the conditioning of fear. As indicated in FIGURE 2, the control animals apparently acquired the stronger CERs early in conditioning, showed the greater generalization to the apparatus (trials C3 and A1), and probably showed somewhat greater resistance to extinction.

Panel C includes, in those instances in which the differences are sufficiently large to be of interest, probabilities[10] for the significance of the differences between the groups in the number of animals that moved during the CS. As scored on the other panels, the data show essentially the same pattern of significant differences when tested, but the criterion of conditioning and the statistical argument as given by the data on panel C are the most stringent.

Although we have interpreted the greater movement scores of the meprobamate group during early conditioning and toward the end of the first seven test-extinction trials as indicating that the CER was weaker than among the control animals, an alternative interpretation is possible and should be considered. The differences between the groups could be attributed to some stimulating effect of the drug that would make the experimental animals more active in general. Such an interpretation would not be inconsistent with the data given in FIGURE 1, where such an effect could have militated against the decline in lever pressing that the hot weather otherwise would have produced.

The data from test-extinction trials 8 through 11, however, argue strongly against this interpretation. Medication was terminated 6 days prior to T8, yet on all of these final test runs the experimental animals showed weaker CERs than the control rats, as indicated by movement scores. The difference between the groups in scores for movement during the CS, summed over trials T8 through T11, is statistically significant ($P = 0.035$, with the distributions dichotomized at the joint median).[10] While the differences between the groups during trials C1 through C9 and T1 through T7 could reflect the effects of meprobamate on activity rather than on the CER, it is unlikely that such effects would have persisted to the 7th through the 10th days after the last medication to account for the differences that appeared in trials T8 through T11.[11]

Accordingly, we interpret the data for the final test trials as indicating that the CS had less suppressant effect on movement—that the residual CERs were weaker—among the experimental than among the control animals. Whether this result reflects a tendency for meprobamate to interfere with and thus to mitigate CER conditioning, or whether the drug facilitates extinction, cannot be determined from the present experiment.

A more recent study,[11] with the CER conditioning and tests carried out in accordance with the standard procedure in the lever-pressing apparatus,[2, 5] has provided some confirmation of these findings. In this study, naïve male albino rats, 50 to 70 days of age at the beginning of the experiment, were put on a 23½-hour water-deprivation schedule and trained to press the lever for the standard aperiodic water reward. After lever pressing had stabilized, all

animals received a total of 5 CER conditioning trials during regular lever-pressing runs. In each conditioning trial the CS was introduced at the beginning of the 4th min. of the 9-min. run and was terminated with 2 momentary, 1.0 mAmp. shocks to the feet at the end of the 6th min. All conditioning trials were separated by at least 1 (usually 2 or 3) 9-min. adaptation runs in the apparatus, without CS or shocks, to favor the development of a well-discriminated CER. Then all animals had a week without runs in the apparatus, but with free access to food and water in the home cages. During this period, as part of their service as control animals in another experiment, all received a total of 14 pseudo-ECS treatments in which the animals were handled and had electrodes clipped briefly to their ears. By itself, this procedure has never had any discernible effect on the CER,[5] but it is mentioned here for the sake of completeness.

At the end of this period the animals were divided randomly into 2 groups of 8 each and were placed on the 23½-hour water-deprivation schedule. The rats in the experimental group received daily, intramuscular, 240-mg./kg. injections of meprobamate, and the control animals received equivalent saline injections. After 4 days of this medication all animals had a 9-min. adaptation run in the lever apparatus without CS or shocks. On each of the succeeding days all animals had a daily test-extinction run in the lever apparatus, which consisted of an unreinforced presentation of the CS during the second 3-min. segment of the run, just as in conditioning. The lever-pressing runs followed the daily injections by 90 to 120 min.

Because of artifacts produced by side effects of the injection procedure, we are reluctant to interpret the data from all the test-extinction runs after the first, T1. On the basis of our experience with the previous experiment, we did not anticipate complications of this sort and we failed to take account of the fact that the total amount of fluid injected would have to be tripled to provide for the larger dose. By trial T2, all animals had received a total of 3 or 4 comparatively large injections of fluid into the muscle of each rear leg. Many appeared to develop a lameness that had an adverse effect on lever pressing, increasing its variation from animal to animal and from trial to trial. Further, a number of the meprobamate animals developed induration and inflammation of the leg muscles that we suspect may have interfered with or otherwise influenced the rate of absorption of the drug.

The data through trial T1, however, are consistent and interpretable and appear in FIGURE 3. Panel A shows the mean inflection ratios for each group for the 5th and last conditioning trial (no medication) and for the first test-extinction trial (after 5 days of medication or placebo and after the adaptation run). As indicated before, the inflection ratio gives the per cent of suppression of lever responses produced by presentation of the CS, with lever pressing output during the 3 min. prior to the introduction of the CS as the denominator. On C5, prior to medication, both groups showed equally strong CERs; after 5 days of medication with meprobamate, the experimental animals showed a substantially weaker CER, while the control group, on placebo, showed CERs of essentially undiminished strength.

Panels B and C show that this difference on T1 is not attributable to a general

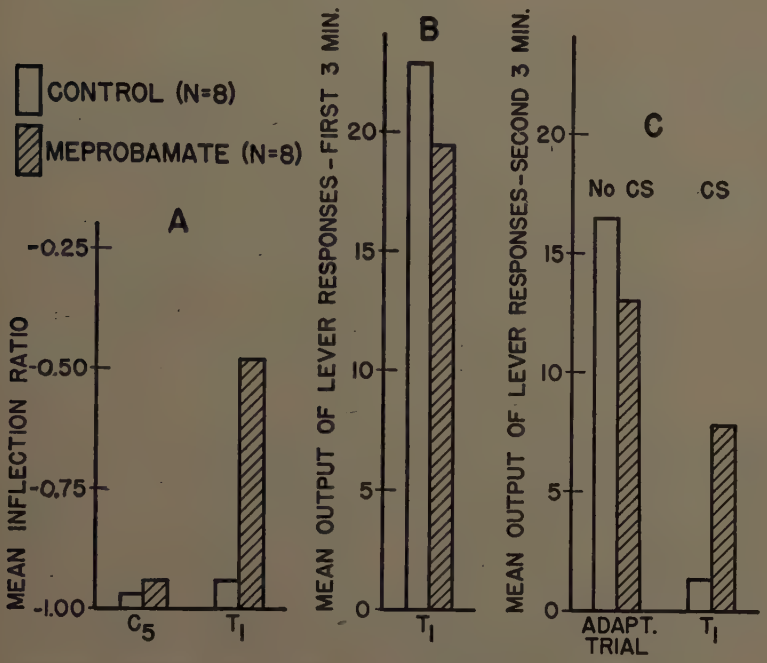

FIGURE 3. Effect of meprobamate on a CER established in the lever apparatus.

increase in lever-pressing output among the experimental animals. Panel B shows that, on T1, both groups made about the same number of lever responses during the 3-min. segment of the run prior to presentation of the CS. Panel C shows directly the suppressant effects of the CS for each group by comparing the output of lever responses during the 3-min. CS with the output during the equivalent 3-min. segment of the adaptation run on the day before. The decrease in output during the CS was significant for the control group ($P < 0.01$), but did not even approach significance for the animals on meprobamate ($P = 0.36$).[10] The difference between the groups in the number of animals defecating during T1 (8 control versus 3 experimental) is consistent with the data on lever-pressing output and is statistically significant ($P = 0.013$).[10] Since the 2 groups differed neither appreciably nor significantly in the incidence of defecation during the preceding adaptation trial (2 control versus 3 experimental), the increase in defecation among the control rats on T1 should be attributed to the presentation of the CS and to the emotional disturbance it evoked.[12] The experimental animals were not disturbed as much during T1, presumably because of the action of the drug.

FIGURE 3 should not be interpreted as indicating that meprobamate completely offset the effects of CER conditioning, however. On T1 the CS still reduced the output of lever pressing by almost 50 per cent. From our normative data,[13] the standard deviation for the inflection ratio in unconditioned rats is ± 0.25 to ± 0.27, with a mean only slightly negative from 0; these experi-

mental animals cannot be considered to have returned to "normal," even though their CERs were, on the average, weakened by the drug.

Meprobamate thus does not appear to block decisively the acquisition, the extinction, or the symptomatic expression of the CER, even in the large doses employed here. However, it does have a subtle but consistent effect antagonistic to the CER that appears during the early and intermediate phases of conditioning an extinction. Whether this effect reflects muscular relaxation or some direct effect of the drug on the conditioning cannot be determined at present. Our previous experience with electroconvulsive shock leads us to expect that the drug effect is quantitative and that it either can be brought out more clearly or obscured altogether by appropriate variations in the parameters of conditioning, such as strength of shock, distribution of trials, and the like. Present research is attempting to identify those variations that are effective in this regard, in the hope of learning how the drug influences conditioned fear.

In addition to the experiments on conditioned fear, we have begun to explore the effects of meprobamate on irritability produced by stereotaxically placed, bilateral electrolytic lesions in the septal forebrain.[14] Several years ago Brady and Nauta[15] reported that such lesions produced, within 24 to 48 hours, a striking savageness and irritability that persisted for some 12 to 14 days. Operated rats show a characteristic attack posture when stimulated tactually with a probe or with another rat, a reduced threshold for actual attack on the disturbing object, an exaggerated startle response usually followed by frenzied running in the home cage on stimulation with a puff of air, and a peculiar hopping gait in locomotion outside the cage. Our observations on the effects of these lesions decisively confirm those reported by Brady and Nauta, including the locus of the effective lesion in those animals on which the histological work has been completed. So far most of our exploration here has been confined to clinical observation and simple tests. At present, we are working on the development of quantitative indicators that will provide objective dose-effect curves.

Meprobamate in doses of 240 mg./kg., given either intramuscularly or orally, dramatically offset septal irritability. The rat was given light ether anesthesia prior to injection to prevent him from injuring himself by struggling to escape or from attacking the experimenter; the observations normally began as soon as the animal started to move about and continued until the effects of the drug had disappeared 3 or 4 hours later. Uniformly, the experimental animals became drowsy and inactive within 30 to 60 min. after oral injection, with a greater range in time of onset after intramuscular injection. These effects persisted for 2 to 4 hours. The affected animals developed a pronounced enophthalmos, poor co-ordination of action in the rear legs, and some decrease in body temperature. Although drowsy and inactive, if left undisturbed they could be aroused easily to move about. They showed clear-cut loss in muscle tonus, were docile, and could be handled easily with the bare hands. Further, they showed a dramatic loss of the startle response to touch and to a puff of air, and only with great difficulty and only in a few cases could they be goaded

into assuming an attack posture or attacking a probe or finger. Usually, no aggressive behavior could be elicited.

In contrast, unoperated rats and rats in which the stereotaxic lesions failed to produce the irritability showed little or no gross changes in behavior under meprobamate at this dose level. Furthermore, rats that had lost the septal irritability did not appear to respond abnormally to the drug and showed about the same reaction as the unoperated control animals. Finally, once the immediate anesthesia had dissipated, neither the ether anesthesia alone nor the vehicle in which the drug was dissolved produced discernible effects on the behavior of operated or control animals.

With several exceptions, the effects of mephenesin were practically identical with those of meprobamate. The duration of action, as would be expected, was somewhat shorter (usually less than an hour). Also, mephenesin appeared to eliminate sensitivity to pain, as indicated by a retraction of the rear legs when the tail was pinched; meprobamate did not do this. Our observations suggested, too, that the drop in body temperature was greater with mephenesin.

Equivalent observations on the effects of chlorpromazine indicated that this drug acted differently. Subcutaneous, 3.75-mg./kg. injections of chlorpromazine produced about equal sedation in all rats—unoperated controls, and operated rats that did or did not develop irritability, with the irritable rats showing somewhat longer intervals between the injection and the onset of sedation. Further, the irritable rats could be aroused as easily as the others and, once aroused, bit and attacked a disturbing probe and could not be handled safely with the bare hands.

The septal lesions, when they produced irritability, also appeared to increase the sensitivity of the rat to meprobamate and mephenesin. The symptomatic sedation produced among these animals resembled that produced in normal rats by much more massive doses of these drugs (on the order of 600 mg./kg.). Since septal irritability was not a normal emotionality, the implication of these preliminary findings for the tranquilizing effects of meprobamate, however dramatic, was obscure. The fact that the sensitivity of the operated animals to meprobamate and to mephenesin developed only if irritability also appeared, however, and disappeared when the irritability disappeared was intriguing and may provide a lead to research that will clarify the mode of action of these drugs in relation to emotion and the limbic system.

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Discussion of the Paper

S. Irwin (*Department of Pharmacology, Schering Corporation, Bloomfield, N. J.*): I think selectivity of action is a rather important point to be looked for in the study of drugs that we claim to be tranquilizers. If anesthetic effect or paralysis is the price we must pay for tranquilizing or sedative action, I am not sure that we are entirely prepared to go along with it. I think one can claim almost any component of a drug's action as a side effect, depending upon our frame of reference. In a tranquilizing drug we are interested in *behavioral specificity*. To be of value, there should be no side actions of an undesirable nature, such as ataxia or paralysis, in the effective dosage range.

H. F. Hunt: We have not yet been able to get satisfactory dose-effect curves. Smaller doses seem to produce lesser effects. I suspect that larger doses given to normal animals will produce very much the same effect as that achieved with mephenesin.

Question: I am impressed with the fact that extrapolation from one animal may be dangerous. According to my calculations, the dosage of chlorpromazine, in terms of milligrams per kilogram, is similar to that used in human beings; doses of meprobamate are about twenty times this dosage.

Question: I should like to know the duration of rage after a lesion is placed.

H. F. Hunt: There is some variation. Usually the animals show irritability within 24 to 48 hr., and it may disappear within a week. We have had some cases that continued for periods of as long as or more than 2 weeks, causing a delay while we waited for them to "cool off" before we could try the postrage test to show that the effect of the drug no longer existed.

Question: Would you reiterate your concept of the difference between meprobamate and chlorpromazine with regard to effects?

H. F. Hunt: In general, chlorpromazine will make the animals quite drowsy if they are left to themselves. The 3.75-mg. dose is similar in effect to the larger dosage of meprobamate. The meprobamate-treated animals cannot be aroused to attack, however. We believe that the behavioral effects of the

operation merely sensitize the animal to meprobamate. We have been surprised by the quantities of meprobamate necessary to produce effect in rats. The quantities were arrived at empirically; we gave as much as was necessary to produce some effect. Chlorpromazine dosages of 10 mg./kg. produced a drowsiness equivalent to that produced by meprobamate. The animal could be conditioned, but was ataxic and unable to move well. It was not arousable in the sense that it could not be made to pay attention even by hitting it on the nose with a ruler, as was possible with the animals treated with meprobamate. We think the two drugs operate in different ways, but we have no idea, at present, as to the specific mechanisms involved.

EFFECTS OF MEPROBAMATE ON IMPRINTING IN WATERFOWL*

By Eckhard H. Hess

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To discuss properly the effects of meprobamate on the imprinting process it is necessary to give an account of the phenomenon of imprinting and the methods with which it is studied in our laboratory. The first section of this paper therefore will give a brief account of our general approach to the problem and the particular results that bear on the present study.

Students of behavior generally agree that the early experiences of the organism have a profound effect upon adult behavior. The literature in this field has recently been reviewed by Beach and Jaynes.[1] Hebb[2] has given us the rule that the effect of early experience upon adult behavior is inversely correlated with age. Our problem, then, is not so much to determine whether early experience is important in determining adult behavior as it is to decide how these results are accomplished.

Three somewhat different statements concerning this problem are usually made in the contemporary literature. The first of these is that early habits are very persistent and may prevent the formation of new ones. The second is that early perceptual learning profoundly affects all future learning. This theory leads to the very difficult problem of whether basic perceptions are inherited or acquired. Experimental procedures used here usually consist of preventing the subject from using some sense modality for a period of time and then comparing his behavior with controls of the same age who have had the opportunity of using that modality. Results are difficult to interpret, as this procedure often results in degenerative changes in the sense organ involved. The third of these statements is that early social contacts determine adult social behavior. This is imprinting.

At the turn of the century, Craig,[3] experimenting with wild pigeons, found that in order to cross two different species it was first necessary to rear the young of one species under the adults of the other. Upon reaching maturity the birds so reared preferred mates of the same species as their foster parents. Other intersexual fixations have been observed in birds and fishes.

Heinroth[4, 5] and his wife successfully reared by hand the young of almost every species of European bird. They found that many of the social responses of these birds were transferred to their human caretaker. Lorenz[6] extended these experiments, dealing especially with graylag geese. Lorenz also was the first to point out the fact that there are certain critical periods in the animal's life in which such modification of behavior occurs. Ramsay and Hess[7] have found the critical age for the imprinting of mallard ducklings on their parents to be at twelve to seventeen hours after hatching. In addition, Lorenz postu-

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lated that, in imprinting, the first object to release a social response becomes the only one to release at maturity not only that particular response, but other related social responses. As has been pointed out repeatedly in the literature, then, imprinting is not only related to the problem of behavior, but also to the general biological problem of evolution and speciation.

Although studied mainly in birds,[8, 9] examples of imprinting have been reported in insects,[10] in fish,[11] and in some mammals. Those mammals in which the phenomenon has been reported (sheep,[12] deer,[13] and buffalo[14]) are all animals in which the young are almost immediately mobile when born. Experimental work with mammals has, however, not been done within the framework presented here.

Genetic studies with two species of fowl that I began in 1955 now indicate that imprintability is inherited and can be bred into or out of a strain. Further experiments with cochin bantams indicate that the inheritance of imprintability is probably sex-linked.

Briefly then, imprinting has been represented as an extremely rapid form of learning that takes place in the early life of many organisms and that is possible only during a very brief period in the life of those organisms.

Testing Procedure

Subjects. The subjects were mallard ducklings, although similar experiments were also carried out with other species of fowl.

Apparatus. The apparatus we constructed to be used in imprinting consisted of a circular runway about 5 ft. in diameter. This runway was 12 in. wide and 12½ ft. in circumference at the center. Boundaries were formed by walls of Plexiglas 12 in. high. A mallard duck decoy, suspended from an elevated arm radiating from the center of the apparatus, was fitted internally with a loud-speaker and a heating element. It was held about 2 in. above the center of the runway. The arms suspending the decoy could be rotated by either one of 2 variable-speed motors. The speed of rotation and intermittent movement could be regulated from the control panel located about 5 feet from the apparatus. The number of rotations of both the decoy and the animal were recorded automatically. Tape recorders with continuous tapes provided the sound that was played through the speaker of the decoy. A trap door in the runway, actuated from the control panel, would return the duckling to its box.

Preliminary procedure. Mallard eggs were collected from nest boxes located in a duck-pond area. After storage for a few days, they were incubated in a dark forced-air incubator. About 2 days before hatching, the eggs were transferred to a hatching incubator. Precautions were taken to place each newly hatched bird into a small cardboard box (5 × 4 × 4 in.) in such a way that little visual experience was possible in the dim light used to carry out this procedure.

Each bird was given a number that was recorded on the box itself, as well as in our permanent records. The boxes, each containing its bird, were then placed in a still-air incubator, used as a brooder, and kept there until the birds were to be imprinted. After imprinting, each bird was automatically returned

to its box, and the box was then transferred to a fourth incubator, also used as a brooder, and kept there until the bird was to be tested.

Imprinting procedure. A certain number of hours after hatching, the young mallard was taken in its box from the incubator and placed in the runway of the apparatus. At this time the decoy was situated about 1 ft. away. By means of a cord, pulley, and clip arrangement the observer released the bird and removed the box. As the bird was released, the sound was turned on in the decoy model and, after a short interval, the decoy began to move about the circular runway. The sound used in the imprinting of the mallard ducklings was an arbitrarily chosen human rendition of "GOCK, gock, gock, gock, gock." The decoy sounded this call continually during the imprinting process. The duckling was allowed to remain in the apparatus for a specified amount of time while making a certain number of turns in the runway. At the end of the imprinting period, which was usually less than 1 hr., the duckling was automatically returned to its box and placed in an incubator until it would be tested at a later hour for imprinting strength.

Testing for imprinting. Each duckling to be tested was mechanically released from its box halfway between 2 duck models placed 4 ft. apart. One of these was the male mallard model upon which the test duckling had been imprinted; the other was a female model that differed from the male only in its coloration. One minute was allowed for the duckling to make a decisive response to the silent models. At the end of this time, regardless of the nature of the duckling's response, sound was turned on simultaneously with each of the models. The male model made the "GOCK" call upon which the duckling had been imprinted, while the female model gave the call of a mallard duck calling her young. The 4 test conditions following in immediate succession were: (1) both models stationary and silent; (2) both models stationary and calling; (3) male stationary and female moving, both calling; and (4) male stationary and silent, female moving and calling. Scores in percentage of positive responses were then recorded for each animal.

Experiment I: The Critical Age for Imprinting in Mallards

Ducklings were imprinted at various hours after hatching in an effort to determine the age at which an imprinting experience of 10 min. with a "following" response of about 150 to 200 ft. was maximally effective. The results were determined initially in 1953, but were substantiated and enlarged upon in 1954. Some imprinting appears possible almost immediately after hatching, but a maximum score is consistently made only by those ducklings imprinted in the 13- to 16-hr. group. This result is indicated in FIGURE 1.

Another way in which we can look at these data would be to consider only the number of animals in each age group (grouped by 4-hr. intervals) that make perfect scores, that is, that respond positively to all aspects of the test situation. When plotting the percentages for such "completely imprinted" animals, we find an even sharper peak, indicating that maximum imprinting is easiest in the mallard when imprinting occurs over a brief period at from 15 to 16 hr. after hatching. In our initial groups, no animal imprinted at less than 12 hr. or more than 16 hr. made a perfect score. Additional data ob-

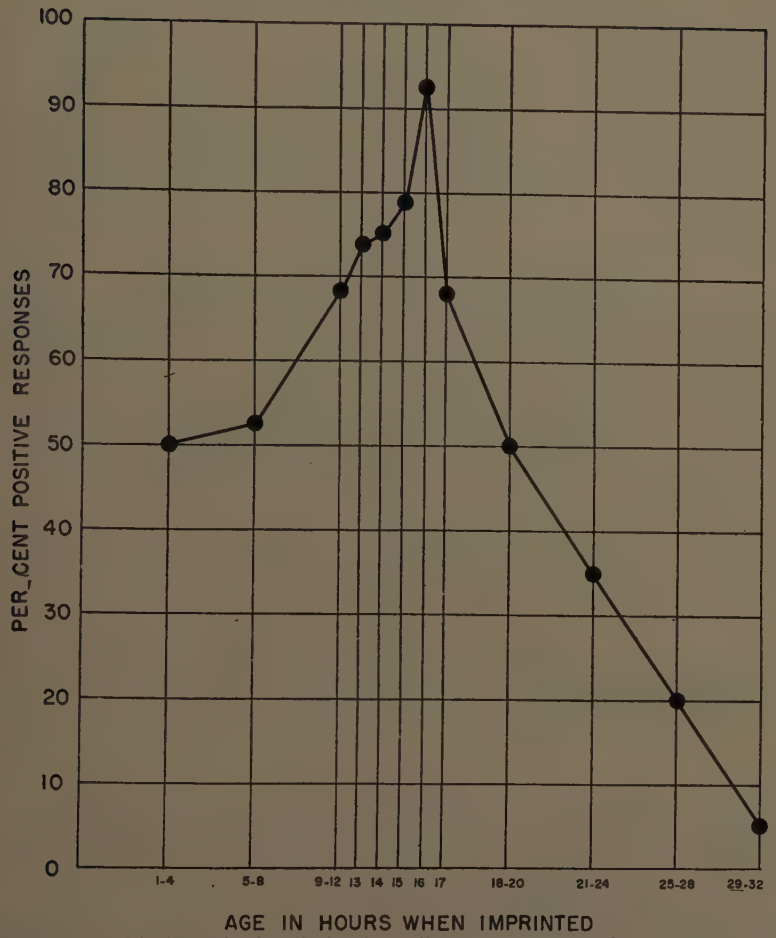

FIGURE 1. Critical age for imprinting in mallards expressed as the per cent of positive responses.

tained in 1954 indicate that the optimal age is closer to 16 hr., building gradually up to that point and then falling sharply after about 17 hr. The test results of the critical age for optimal imprinting are shown in FIGURE 2.

Experiment II: Imprinting Strength as a Function of Distance Traveled

In an effort to determine how long an imprinting experience must last to be maximally effective, we decided independently to vary the factors of time of exposure and the actual distance traveled by the duckling during the imprinting period. Since previous results had indicated that a 10-min. exposure period was sufficient to produce testable results, we decided to run a series of tests using varying distances but keeping the time constant at 10 min. We therefore used 1 circumference of the runway (12½ ft.) as a unit and ran

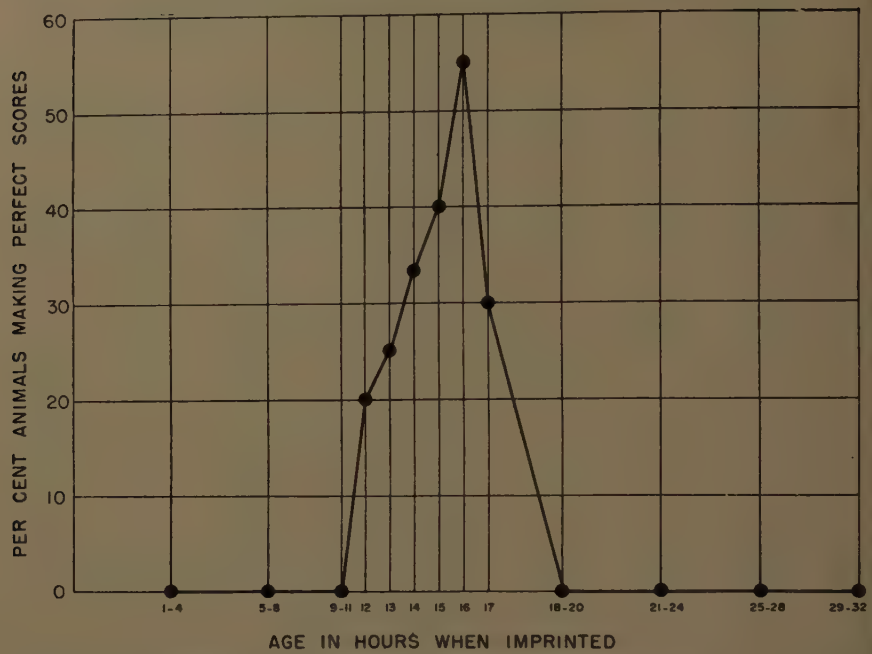

FIGURE 2. Critical age for imprinting in mallards expressed as the per cent of animals making perfect scores.

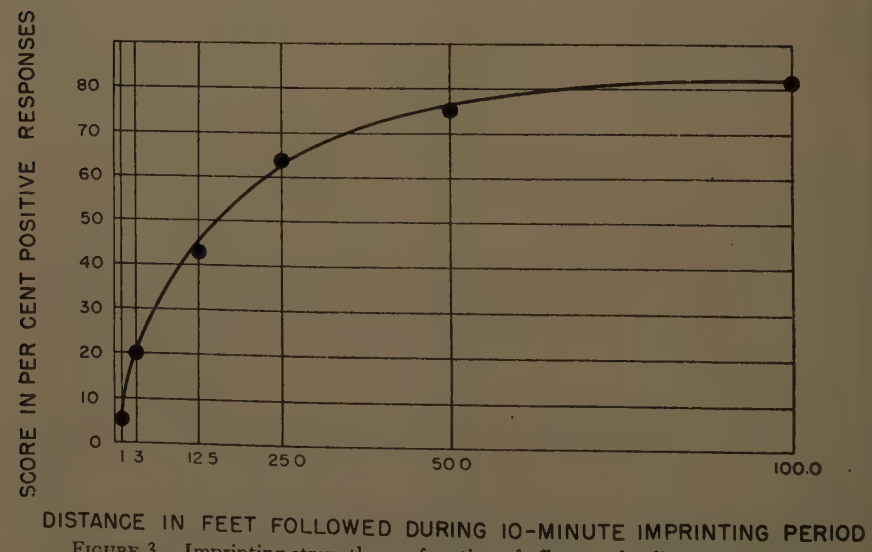

FIGURE 3. Imprinting strength as a function of effort or the distance traveled.

groups of animals for 0, 1, 2, 4, and 8 turns. This resulted in imprinting experiences in which the ducklings moved about 1 ft., and 12½, 25, 50, and 100 ft., respectively. All ducklings were imprinted between 12 and 17 hr. of age in order to keep the variable of the critical period constant. The results showed that increasing the distance over which the duckling had to follow the imprinting object increased the imprinting strength. A leveling off of this effect appeared to occur after a distance of about 50 ft. These results are shown in FIGURE 3.

Experiment III: Imprinting Strength as a Function of Exposure Time

In order to determine the effect of the length of the exposure time on imprinting strength, we chose a distance that could be traversed by ducklings in periods of time as short as 2, 10, and 30 min. Scores made by animals imprinted for these 3 time periods, while traveling a distance of 12½ ft., were essentially identical. There was also no significant difference between the scores of ducklings allowed to follow for a distance of 100 ft. during 10 min. and those allowed 30 min. to cover the same distance. Both of these results are shown in FIGURE 4. The results for 50 ft. are also shown. These scores fall between the ones for 12½ and 100 ft.

Drug Experiments

The previously mentioned experiments show, first, that there is a well-defined maximum period when imprinting can best take place and, second, that

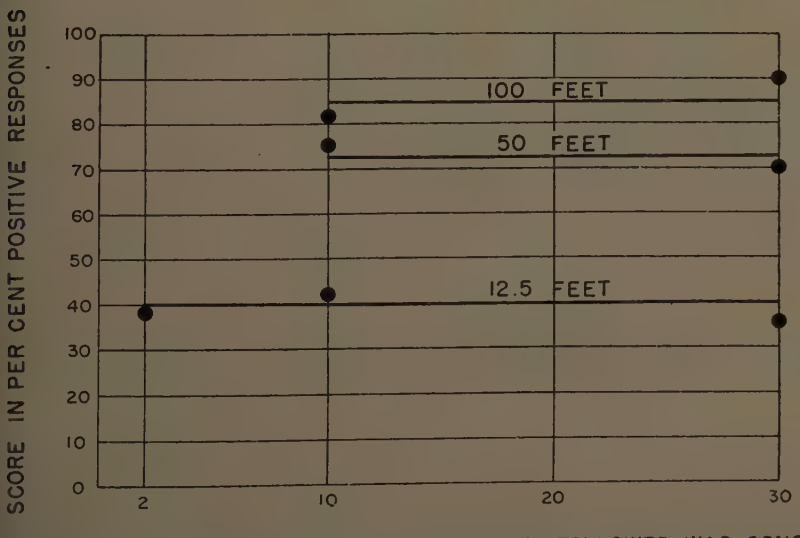

FIGURE 4. Imprinting strength as a function of exposure time during the imprinting period.

the strength of imprinting is related directly to the effort expended by the duckling in getting to or keeping up with the imprinting object. In addition, it should be mentioned that emotional responses on the part of the ducklings begin to appear when they are about 20 hr. old. This response is a fear or avoidance of any moving object in the environment. It is probable that the rapid drop in imprintability is coupled with this developing emotional response—a response that makes imprinting impossible. Almost 80 per cent of the 24-hr.-old ducklings show this fear response, and the percentage increases rapidly to 100 at about 32 hr. or older. To examine this aspect of imprinting, it seemed logical to reduce the emotional response by the use of a tranquilizing drug. Meprobamate was chosen because of evidence that it would reduce emotionality without markedly influencing motility or co-ordination. Preliminary experiments with dosages of 14 to 30 mg./kg. of body weight showed clearly that the emotionality of the duckling was markedly reduced. In fact, the duckling showed no fear of strange objects or persons, even though he was at an age when marked fear is normally a certainty. The effectiveness of meprobamate, introduced orally, was noticeable after about 20 min. and disappeared in about 5 hr.

To obtain the maximal information from this experiment, we then decided to test animals under the 4 following conditions: (1) drug at 12 hr., imprint at 24 hr., test when drug effect had worn off; (2) drug at 12 hr., imprint at 14 to 16 hr., test when drug effect had worn off; (3) imprint at 16 hr., test under drug later; and (4) drug at 24 hr., imprint at 26 hr., test when drug effect had worn off.

In general, the procedure was the same as that mentioned previously. Control animals were given ⅓ c.c. of distilled water, and chlorpromazine and Nembutal were used to obtain additional information. The results are shown in TABLE 1.

It is obvious that, while meprobamate reduces the fear or emotional behavior, it also makes imprinting almost impossible. It does not, however, interfere with the effects of imprinting. This is clear from the results of test 3. Chlorpromazine apparently allows a high degree of imprinting under all conditions, whereas Nembutal reduces imprintability at all points except under the conditions of test 3.

TABLE 1

PER CENT OF POSITIVE RESPONSES MADE BY DUCKLINGS UNDER DIFFERENT CONDITIONS OF TESTING AND DRUG ADMINISTRATION

	Control H_2O	Meprobamate 25 mg./kg.	Nembutal 5 mg./kg.	Chlorpromazine 15 mg./kg.
1. Drug at 12 hours, imprint at 24 hours	14	54	31	57
2. Drug at 12 hours, imprint at 14 to 16 hours	62	8	28	63
3. Imprint without drug at 16 hours, test under drug	61	65	61	58
4. Drug at 24 hours, imprint at 26 hours	19	17	16	59

Conclusions

From the data thus far presented, it appears that we might interpret the action of the drugs as follows. If we assume that meprobamate and chlorpromazine reduce metabolism, then we could expect the high imprinting scores at 24 hr. (test 1), because metabolism had been slowed and we had thus stretched out the imprinting or sensitive period. This did not occur when we used Nembutal or distilled water. The second point deals with the reduction of emotionality. In test 4 we had little evidence of emotionality in the meprobamate and the chlorpromazine group. This did occur in the control and in the Nembutal group. Thus far, the only way we can interpret this former result is to consider the finding of experiment II. Here we found that the strength of imprinting was a function of effort or of distance traveled. It may be that, since meprobamate is a muscle relaxant, these effects of meprobamate cut into the muscular tension or other afferent consequences and thus nullify the effectiveness of the imprinting experience. Since, under the same circumstances, we attain perfectly good imprinting in all cases with chlorpromazine, this notion becomes even more tenable. In an earlier paper, Hunt[15] stated some of these preliminary results and arrived at much the same conclusion in a personal communication. Further studies already in progress are continuing within this framework.

Summary

Briefly, imprinting is an extremely rapid form of learning that can take place only during a very brief period in the early life of some organisms. Mallard ducklings show this effect maximally only between 12 and 17 hr. after hatching. This was expressed experimentally in the mallard ducklings by the rapidity with which they could learn to follow a moving object exposed to them during a brief period of time. The strength of the imprinting effect is directly related to the amount of muscular energy expended by the mallard in getting to, or in following, the object. The amount of exposure time is not relevant.

Using dosages of about 25 mg. of meprobamate per kg. of body weight, the following results have been obtained:

(1) Imprinting of mallards during the critical age (12 to 17 hr.) is almost impossible when the birds are under the influence of the drug. The animals are, however, quite active and behave normally.

(2) Animals imprinted at the critical age without the drug will show the response of following, even though they are tested for following under the standard dosage of meprobamate.

(3) Animals given a standard dose of meprobamate at 24 hr. cannot be imprinted at 26 hr., even though they do not show the fear and avoidance behavior ordinarily exhibited at that age.

(4) Meprobamate appears to extend the critical age for imprinting. Animals given meprobamate at 12 hr. can be imprinted fairly successfully at 24 to 26 hr. when the effect of the drug has worn off.

These results are apparently in accord with the metabolism-lowering and muscle-relaxant effects of meprobamate.

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Discussion of the Paper

Question: What route of administration was used?

E. H. Hess: The oral route. We found that in a very subdued blue light, to which the animals are relatively insensitive, we could get the material down very quickly with a medicine dropper. I should be a little afraid of injection with a needle although, at the same time, the animals were still aware of some contact and knew that something was stirring in the environment.

Julian Huxley (*London, England*): I do not think you gave us the figures of the strength of the imprinting. When the duck had a choice, how often did it follow the figure with which it had been imprinted? I should also like to ask whether you have not tried any other substitute objects.

Hinrod tried various substitute objects; within certain limits it is possible to substitute all kinds of curious things, and this, I think, is one of the strange things about imprinting—that the specificity of sign stimulus, so striking in many animal reactions, is largely, although not entirely, abolished.

E. H. Hess: The strength of imprinting depends on the effort expended. Also, if the imprinting has been done at the critical period, it is possible, under certain conditions, to make it one hundred per cent effective. We have worked with all kinds of substitute objects, but this would be more properly discussed in a meeting concerned with the problems of imprinting, and not with the effects of drugs on the imprinting or learning process.

J. Huxley: You said the imprinting always took place at an early age. I do not think this is necessarily so. In songbirds imprinting does not so take

place. It occurs just when they are a year old or are coming into maturity. This may have some bearing on the fact that human beings are subject to a peculiar form of imprinting known as romantic love. It may take place when they reach puberty. The extremely important point brought out in this paper about imprinting is the fact that there is a critical period and that this period is usually quite brief.

Similar experiments that Scott has been doing on dogs at Bar Harbor have showed that there is a critical period when they can be trained and when they can become accustomed to human beings. If dogs are not tamed they remain wild forever. We have the same sort of thing in human beings, as Hess has said about mother love. Work done by Bulbey in England, and by Spitz in the United States, has shown that, if you deprive the child of the mother or a mother substitute during a critical period, the child will develop an apathy or a lack of moral sense.

I must say that I think this is one of the most interesting pieces of work done on the relationship of drugs and general biology, and I hope very much that it will be continued.

E. H. Hess: I simplified things a bit by saying that imprinting always occurs at an early age. I mentioned Hebb's statement. I think that in some respects he is quite wrong, because I agree with Lorenz that there are probably periods in the lives of some animals during which certain kinds of social imprinting take place. It certainly occurs in the dog when he becomes sexually mature as when, territorially, for example, he may or may not team up with some pack and accept some leader. Of course the experiments by Scott show that, although very little handling is necessary, some human handling must occur between the age of four and seven weeks. If this does not happen the animal will never be a tamable dog. There are very important experiments that deal also with this general area.

COMPARATIVE STUDY OF THE EFFECT OF MEPROBAMATE ON THE CONDITIONED RESPONSE, ON STRYCHNINE AND PENTYLENETETRAZOL THRESHOLDS, ON THE NORMAL ELECTROENCEPHALOGRAM, AND ON POLYSYNAPTIC REFLEXES*

By Carl C. Pfeiffer, Arthur J. Riopelle, Richard P. Smith, Elizabeth H. Jenney, and Harry L. Williams

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Meprobamate has been introduced as a safe prescription drug on the basis of the work of Berger *et al.*[1-3] According to the published data of this group, meprobamate has a striking tranquilizing effect on monkeys, antidotes strychnine, abolishes flexor reflexes, and elevates the pentylenetetrazol threshold. It is also claimed that the drug does not affect the normal electroencephalogram (EEG), or produce sleep waves or barbiturate spindles in the EEG, but that it does produce a synchronization of thalamic recordings from depth electrodes in the cat, where recordings show slowing with greater regularity and higher voltage. Thus, entirely on the findings of a single pharmacological laboratory (as far as we have been able to ascertain from a careful perusal of scientific literature), this drug has been launched into therapeutics as a tranquilizer with muscle relaxant action, that is, a long-acting mephenesin. It therefore behooves other pharmacological investigators to confirm or disprove these claims and to compare the drug to other known internuncial neuronal depressants and central-nervous-system (CNS) drugs. Such a comparison is attempted in this paper.

At present approximately eight (nine, if one includes general anesthetics) different classes of drugs may be recognized by their pharmacological effects on the CNS (TABLE 1). As a first class, the CNS stimulants have been used for centuries. Each of these has individual characteristics, but these will not be discussed in this paper, since no claim has been made that meprobamate is a CNS stimulant. The anticonvulsants, class 2, have been studied since 1857, when bromides were introduced. The epileptologists and the neuropharmacologists have partially classified these in order of efficacy. Class 3, analgesics, can be passed over, since Berger[3] has shown that in animals meprobamate does not exhibit analgesic properties. The barbiturate-alcohol depressants, class 4, have been partially studied, but many more pertinent investigations are needed. The depressant antihistamine-anticholinergic drugs, class 5, are known to produce sedation and sleep, but accurate laboratory data on the site of action are meager. The interneuron-inhibiting drugs, class 6, have been recognized as a class since 1946, when Berger and Bradley[4] described the action of mephenesin. The true ataractic drugs, class 7, are only a few in

* This study was supported in part by Grants Nos. MH-587 and MH-875 from the National Institute of Mental Health of the National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Md.

TABLE 1
CLASSIFICATION OF CNS-ACTING DRUGS

Class 1. Stimulants
Drugs: caffeine, amphetamine, methamphetamine, pipradrol, Ritalin, strychnine, pentylenetetrazol, etc.
Partially classified by neuropharmacologists and neurophysiologists.
The most extensively studied group.
Class 2. Anticonvulsants: these have been partially classified according to efficacy by the epileptologists and by the neuropharmacologists.
Class 3. Analgesics: these have been partially classified according to potency, duration of action, and site of action by the anesthesiologists and pharmacologists.
Class 4. Barbiturate-alcohol depressants
Drugs: barbiturates, alcohol, paraldehyde, chloral
a. Depress reticular potentials
b. Produce depression and coma
c. Raise pentylenetetrazol threshold
d. Raise electrical convulsive threshold
e. Raise strychnine threshold
Class 5. Depressant antihistamine-anticholinergic drugs
Drugs: Phenergan, promazine, diphenhydramine, some local anesthetics, etc.
a. Block action of histamine
b. Block action of acetylcholine
c. Produce sleep waves in EEG of animals
d. Convulsant in high doses in animals
Class 6. Interneuron-blocking drugs
Drugs: mephenesin, mephenesin carbamate, zoxazolamine
a. Specifically raise strychnine threshold
b. Inhibit polysynaptic neuronal pathways
c. Increase primary spike and inhibit afterdischarge in Lloyd preparation
d. Produce muscular relaxation by central action
Class 7. Ataractic drugs (tranquilizers?)
Drugs: chlorpromazine and some *Rauwolfia* alkaloids
a. Produce adrenergic blockade
b. Lower electrical threshold for convulsions
c. Potentiate or leave unchanged reticular potential
d. Inhibit CAR of rat and monkey
e. Some effect in schizophrenia
Class 8. Hallucinogens
Drugs: LSD-25, mescaline, bufotenin, etc.
Mode of action unknown

number, since we should place only chlorpromazine and some of the alkaloids of *Rauwolfia* in this category. Finally, class 8 is composed of the hallucinogens, some new and some old, but still enigmatic.

This classification serves better as a therapeutic guide than does the use of the general terms "central relaxants" or "tranquilizers" (the relaxing or tranquilizing effect of which can be produced at some dose with most drugs, or by physical exercise, or even by a knock-out blow).

Is meprobamate an ataractic drug such as chlorpromazine or reserpine? In our hands, it does not specifically inhibit the conditioned response in either the rat or the monkey (TABLES 2 and 3); also, rather than lower electroshock threshold, the drug is reported by Berger[1] to elevate this threshold slightly. Thus, we should not expect meprobamate to exhibit the same type of anti-schizophrenic activity as does reserpine or chlorpromazine. Clinical reports, however, claim that psychotics show improvement in behavior while on this drug.

TABLE 2

CONDITIONED RESPONSE IN RATS BEFORE AND AFTER ORAL MEPROBAMATE

Time/Dose	Male rat 190 gm.		Female rate 150 gm.		Male rat 185 gm.		Female rat 215 gm.		Male rat 195 gm.	
	100 mg./kg.	200 mg./kg. 5 hr. later	100 mg./kg.	200 mg./kg. 5 hr later	150 mg./kg.	200 mg./kg. 5 hr. later	150 mg./kg.	200 mg./kg. 5 hr. later	150 mg./kg.	100 mg./kg. 1 hr. later
Predose....	25/25		24/25		24/25		23/25		24/25	
1 hr. post..	24/25	24/25	24/25	23/25	22/25	24/25	24/25	24/25	25/25	25/25
3 hr. post..	25/25	24/25	24/25	25/25	24/25	23/25	24/25	23/25		25/25
6 hr. post..										25/25
24 hr. post.		24/25		25/25		24/25		24/25		24/25

One hundred mg./kg. oral—rats show no signs of neurological deficit.

One hundred and fifty mg./kg. oral—two thirds of the rats showed sedation and slight ataxia.

Two hundred mg./kg. 5 hours after the initial dose produced marked sedation in all rats for more than 3 hours. The animals fell asleep between runs up the pole. Their responses occurred in spite of the fact that they frequently fell from the pole because of sedation and ataxia.

TABLE 3

EFFECT OF DRUGS ON THE CONDITIONED AVOIDANCE RESPONSE OF THE MONKEY*

Drug	Dose mg./kg.	Per cent conditioned responses				
		1 hr.	2 hr.	4 hr.	6 hr.	10 hr.
Azacyclonol	20 I.V.	—	100	100	100	—
Meprobamate	100 oral	—	100	100	—	—
Meprobamate	200 oral	—	84	100	—	—
Pentobarbital	12 I.V.	81	100	—	—	—
Reserpine	0.5 I.M.	—	60	25	17	40
11-Desmethoxyreserpine	0.5 I.M.	—	5	2	1	0
Rescinnamine	0.5 I.M.	—	90	51	17	5
Chlorpromazine	1.0 I.M.	30	0	0	50	100

* Four young Java monkeys (*Macaca cynomolgus*), weighing between 2 and 3 kg., proficient to a criterion of 20/20 conditioned avoidance responses in a wooden shuttle box through repeated practice sessions, were used in this experiment.[13] Reserpine, 11-desmethoxyreserpine, rescinnamine, and chlorpromazine specifically inhibit the conditioned avoidance response; the other drugs do not. Twenty mg./kg. of azacyclonol and 100 mg./kg. of meprobamate failed to produce any observable change in cage behavior or any decrement in the conditioned avoidance response. In all the monkeys, 200 mg./kg. of meprobamate produced ataxia ranging from a slight unsteadiness in locomotion and climbing to complete inability to maintain a normal sitting posture without the use of the hands for added support. In general, these animals resembled monkeys given an ataxia-producing dose of a barbiturate, rather than animals treated with reserpine or chlorpromazine. The taming effect was less pronounced, and catatoniclike postures that accompanied treatment with reserpine or chlorpromazine were not encountered. Any loss of conditioned avoidance responses may be attributed to the ataxia produced by meprobamate rather than to a primary drug effect.

Does meprobamate have the qualities of a barbiturate-alcohol? Careful comparative assays of the pentylenetetrazol and strychnine threshold-raising effects of meprobamate in mice show that, in its pharmacological action, it resembles phenobarbital, or even trimethadione, much more than it does mephenesin (FIGURES 1 and 2; TABLES 4 and 5). In attempting to confirm

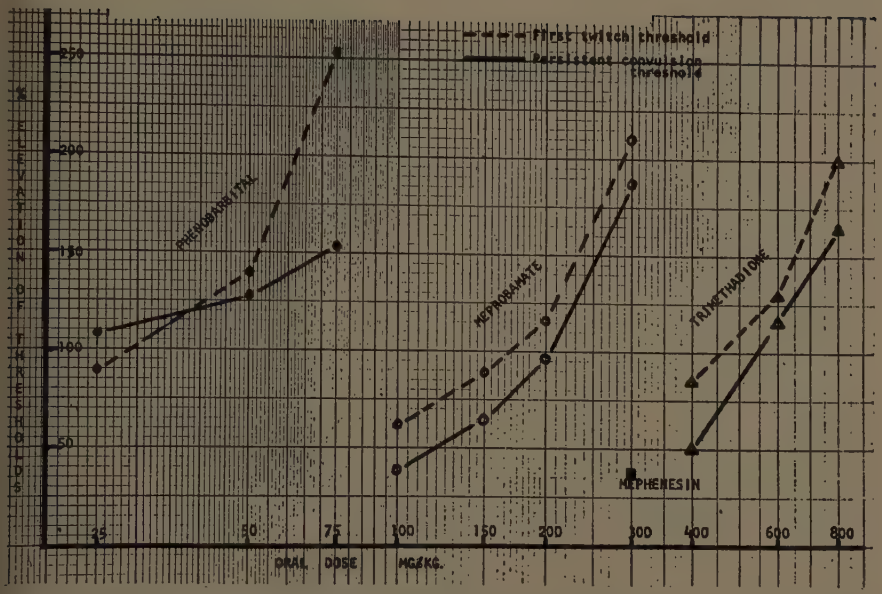

FIGURE 1. Timed intravenous infusion of 0.5 per cent pentylenetetrazol 1 hr. after oral doses of phenobarbital, trimethadione, and meprobamate, and 10 min. after a single oral dose of mephenesin. Pentylenetetrazol was infused intravenously at the rate of 0.05 ml./10 sec. The percentage of rise in the threshold is compared to that of the control mice of the same age and weight. The slope of the meprobamate curve is most similar to that of trimethadione, and the effect on the first twitch and persistent convulsion also mimics trimethadione. Phenobarbital alters the seizure pattern as shown by TABLE 4 and by the unparalleled nature of the curves of the 2 thresholds. Mephenesin has little effect on pentylenetetrazol threshold.

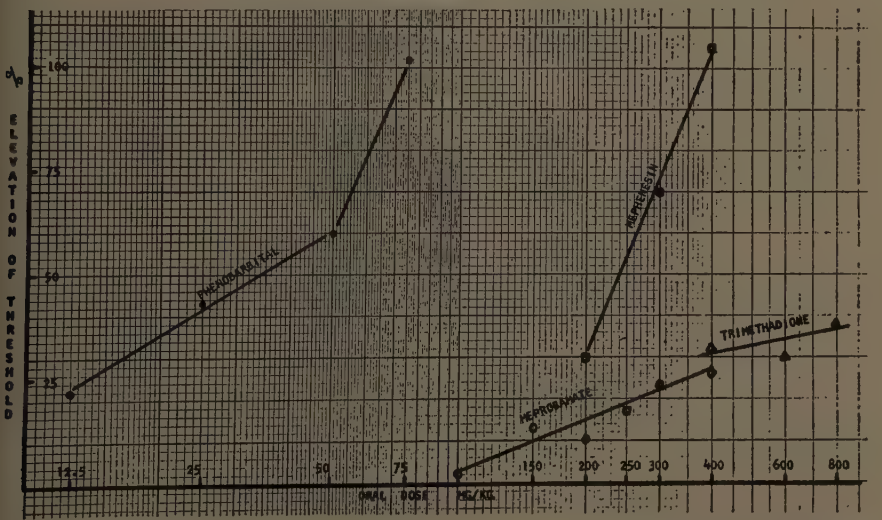

FIGURE 2. Timed intravenous infusion of 0.005 per cent strychnine 1 hr. after oral doses of phenobarbital, trimethadione, and meprobamate, and 10 min. after oral doses of mephenesin. Strychnine was infused intravenously at the rate of 0.05 ml./10 sec. until each mouse had a tonic extensor seizure.[14] The percentage of rise in the threshold is compared to that of the control mice of the same weight and age. The slope of the drug-response curve is steepest with mephenesin and is mimicked by phenobarbital. The meprobamate curve has a low slope similar to that of trimethadione.

TABLE 4

ANTIPENTYLENETETRAZOL ACTIVITY OF MEPROBAMATE AND CONTROL DRUGS*

Dose (oral) mg./kg.	Time	Per cent elevation of thresholds		Type seizure			Mortality per cent	
		FT	PC	TE	TF	Cl		
Meprobamate								
100	1 hr.	62	38	7	1	0	100	8/8
150	1 hr.	89	65	7	1	0	100	8/8
200	1 hr.	116	96	6	1	2	87.5	7/8
300	1 hr.	210	187	3	6	7	94	15/16
400	3 hr.	154	92	5	3	0	100	8/8
400	4 hr.	84	53	8	0	0	100	8/8
400	5 hr.	46	42	8	0	0	100	8/8
Phenobarbital								
25	1 hr.	90	109	2	4	2	100	8/8
50	1 hr.	140	129	0	5	3	87.5	7/8
75	1 hr.	253	153	0	0	8	50	4/8
Trimethadione								
400	1 hr.	85	50	8	0	0	100	8/8
600	1 hr.	130	117	8	0	0	100	8/8
800	1 hr.	200	164	5	2	1	100	8/8
Mephenesin								
300	10 min.	38	35	Clonic			100	20/20

* See FIGURE 1 for the methods used.

TABLE 5

ANTISTRYCHNINE ACTIVITY OF MEPROBAMATE AND CONTROL DRUGS*

Dose (oral) mg./kg.	Time	Per cent elevation of threshold	Mortality per cent	
Meprobamate				
100	1 hr.	2	100	6/6
150	1 hr.	13	33	4/12
200	1 hr.	10	67	8/12
250	1 hr.	17	17	1/6
300	1 hr.	23	17	3/18
400	1 hr.	26	0	0/18
400	2 hr.	34	33	2/6
400	3 hr.	23	0	0/6
400	4 hr.	6	0	0/6
Phenobarbital				
12.5	1 hr.	22	92	11/12
25.0	1 hr.	43	100	6/6
50.0	1 hr.	60	33	2/6
75.0	1 hr.	102	17	1/6
Trimethadione				
400	1 hr.	32	100	6/6
600	1 hr.	30	67	4/6
800	1 hr.	38	50	3/6
Mephenesin				
200	10 min.	30	42	5/12
300	10 min.	70	30	6/20
400	10 min.	105	0	0/12

* See FIGURE 2 for the method used.

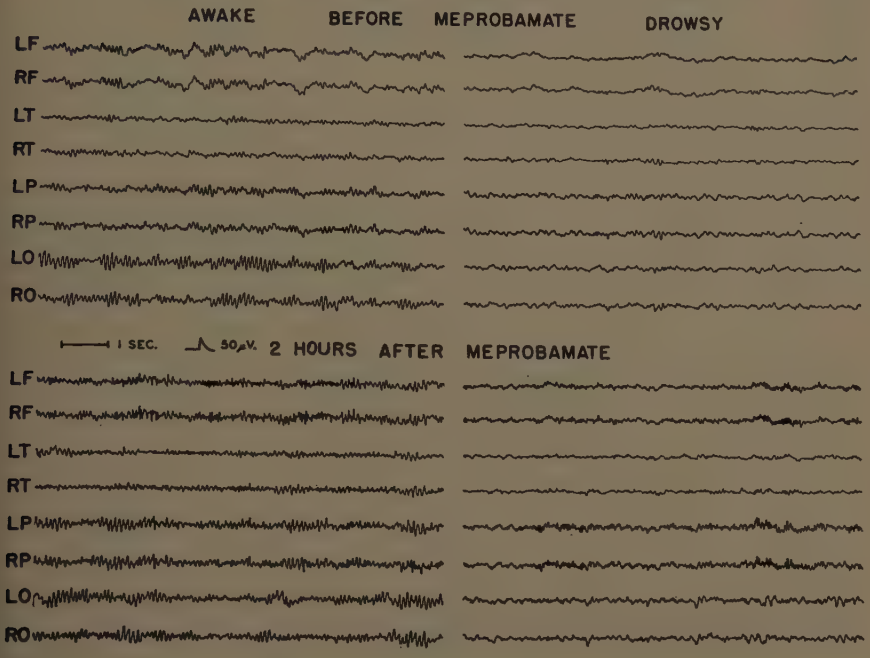

FIGURE 3. Normal, 15-year-old, 145-lb. adolescent male. Before the administration of meprobamate, and while the subject was awake, the EEG showed high-voltage, dominant, 10-per-sec. activity in all areas, maximal in the occipital areas. While the subject was drowsy there was a flattening of activity, with 4- to 5-per-sec. waves of low amplitude. After an oral dose of 1.6 gm. of meprobamate there was no change in the frequency of the dominant 10-per-sec. activity, but the waves have a spiky appearance. Forty minutes after the administration of the drug, bursts of low-voltage, 20- to 30-per-sec. activity appeared, maximal in the bifrontal and biparietal areas. These bursts became more prominent during drowsiness and disappeared during sleep. The patient fell into deep sleep 1 hour after the drug was given. This fast activity in the frontal and parietal areas was frequently seen in the EEG following barbiturate medication. Voltage calibration: 7 mm. deflection for 50 μv.

this barbituratelike action, we have now recorded electroencephalograms on 3 normal human subjects (FIGURES 3, 4, and 5) and have found that a single oral dose of 1600 to 2000 mg. will produce, after a latent period of 40 minutes to 1 hour, a characteristic pattern of almost continuous fast 20 to 30/sec. low-voltage activity in the waking and drowsy record. This fast activity resembles that produced by a dose of 200 mg. of secobarbital and, like the fast activity induced by secobarbital, it disappears during sleep. This is surprising, since Berger reports[3] that "a healthy male subject of 31 years took 8 tablets within 1 hour. There were no changes in his electroencephalogram. Thus, it would be incorrect to call meprobamate a hypnotic." The rise in pentylenetetrazol thresholds after treatment with meprobamate is characteristic of barbituratelike action, and the published report of a *grand mal* seizure when meprobamate was suddenly discontinued[5, 6] is again characteristic of barbiturate action. *Grand mal* seizures in patients discontinuing meprobamate are probably more common than the published reports would indicate. These findings are in

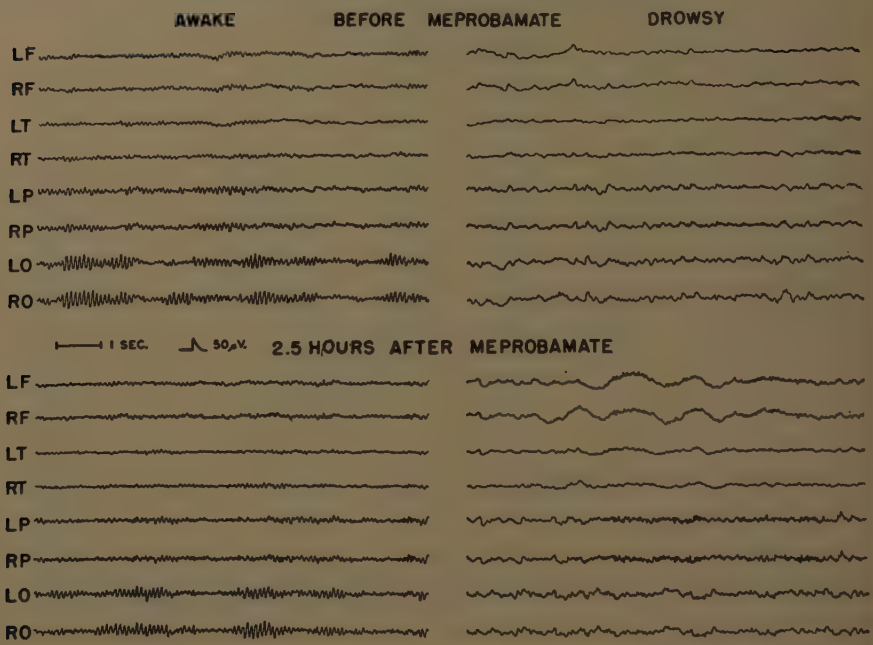

FIGURE 4. Normal, 24-year-old, 145-lb. adult male. Before the administration of meprobamate, and while the patient was awake, the EEG showed moderate-voltage, dominant, 10-per-sec. activity, maximal in the occipital areas. While the subject was drowsy there was a flattening of activity, with 4-per-sec. waves of low amplitude and infrequent bursts of low-voltage, 20-per-sec. activity in the parietal areas. These bursts of fast activity persisted during the parietal hump stage of light sleep. The subject fell asleep in 37 min. without medication. Approximately 1 hour after an oral dose of 2 gm. of meprobamate, 25- to 30-per-sec., low-voltage activity, maximal in the biparietal areas, began to appear in the waking record. This fast activity was more prominent during drowsiness. The subject fell into light sleep 70 min. after administration of the drug and awoke spontaneously 6 min. later. He remained in a drowsy, nonspindle stage for another 70 min., when he fell asleep again.

contrast to the report of Selling,[7, 8] who finds no tolerance to meprobamate, and no withdrawal syndrome when the drug is abruptly discontinued. Also, Perlstein,[9] in his treatment of epileptics, was apparently able in each of his patients to substitute a placebo abruptly without increasing the incidence of *grand mal* seizures or precipitating status epilepticus. If meprobamate is barbituratelike and is effective in epilepsy, then the "all or none" substitution of placebo capsules, as claimed by Perlstein, should have been a dangerous procedure. Perlstein also made electroencephalographic studies to determine whether or not meprobamate normalizes the characteristic EEG of *petit mal*. He reports that this drug was not as effective as trimethadione in this respect.

Is meprobamate antihistaminic or atropinelike? Nothing in Berger's published reports[1, 3] would lead one to suspect that any of its pharmacological actions are similar to those of a depressant antihistamine drug.

Is meprobamate a potent depressant of internuncial neurons? Data from this laboratory (FIGURE 2) show that, in comparison with phenobarbital and

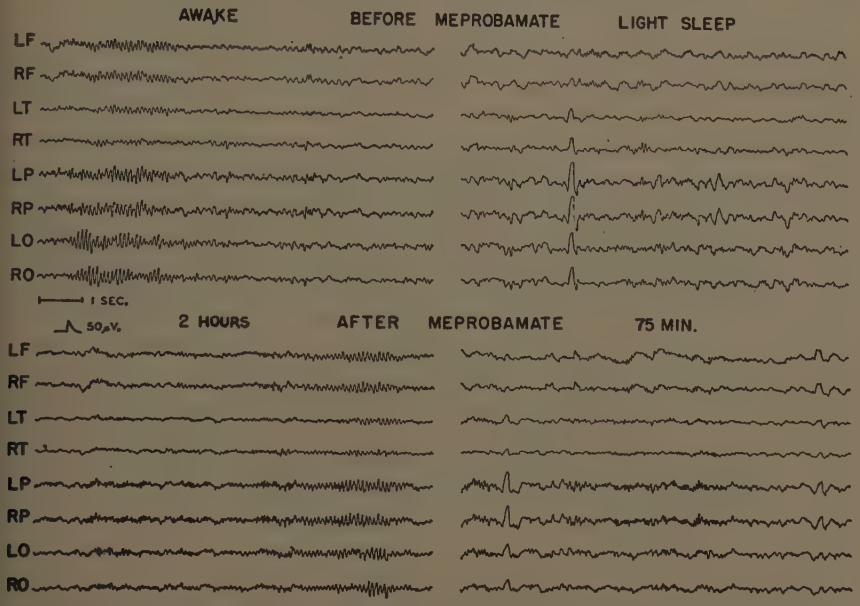

FIGURE 5. Normal, 30-year-old, 143-lb. adult male. Before the administration of meprobamate, and while he was awake, the EEG showed moderate-voltage, dominant, 11-per-sec. activity maximal in the occipital areas, and some 5- to 6-per-sec., low-voltage waves maximal in the bifrontal and the biparietal areas. The subject fell into a light sleep in 27 min. without medication. During the parietal hump stage there was a small amount of 20- to 25-per-sec., low-voltage activity maximal in the biparietal areas. Forty-four min. after the administration of an oral dose of 2 gm. of meprobamate, 25-per-sec. activity appeared in the waking record. The subject reached the parietal hump stage of light sleep in 67 min. At this time there was a marked increase in the fast frequencies—bifrontal and biparietal. At the end of 2 hr. there was almost continuous low-voltage fast activity during the waking and the drowsy periods. Voltage calibration: 7 mm. deflection for 50 μv.

mephenesin, it is a poor antidote for strychnine convulsions in the white mouse. Berger,[1] however, reports that "the effectiveness of meprobamate in preventing strychnine convulsions was similar to that of mephenesin. Meprobamate was, however, more effective than mephenesin in preventing death from toxic doses of strychnine." In addition to this effect against strychnine toxicity, Berger[1] reports that, regarding the effect of meprobamate on the direct and flexor reflexes of the chloralosed cat, 40 mg./kg. decreased the direct reflex and completely inhibited the flexor reflex. In spinal cats in our laboratory, the threshold for equivalent pharmacological action of the 3 drugs is 10 mg./kg. for phenobarbital, 20 mg./kg. for mephenesin, and 40 mg./kg. for meprobamate. Thus, mephenesin is twice as potent, and phenobarbital can be considered to have a fourfold greater muscular-relaxant effect than meprobamate.

Is meprobamate classifiable in one or more of the known categories, or is it pharmacologically unique? We found that normal subjects taking single oral doses of the drug showed increased motor activity during sleep. In the case of one young lady, her room-mate reported that after 4 tablets she was "like an eel all night long, sound asleep, but all over the double bed." This was also

apparent in other subjects whose EEGs were being recorded during sleep. In contrast, secobarbital, used to induce sleep for electroencephalographic purposes, does not cause a heightened motor activity during the peak of drug action.

We find that meprobamate raises the pentylenetetrazol threshold in a dose-action curve in a way similar to that of trimethadione or phenobarbital. It produces barbituratelike fast activity in the EEG of the normal subject. It mimics neither mephenesin nor phenobarbital in its dose-action curve against strychnine. Its duration of action is more similar to that of phenobarbital than to that of the short-acting barbiturates. Lasagna[10] finds that the onset and duration of sleep produced by 400 and 800 mg. of meprobamate is most comparable to that produced by 100 and 200 mg. of phenobarbital when a placebo, secobarbital, and pentobarbital are used as controls.

We can conclude only that meprobamate has a prolonged barbituratelike depressant action mixed with a moderate degree of trimethadione effect on the brain. Whether this particular combination of known pharmacological actions, plus other unknown effects, is desirable clinically remains to be determined.

Discussion

It is evident that meprobamate is primarily not mephenesinlike, but is best characterized as a sedative of the phenobarbital type that, either by primary action or by action of its degradation products, produces a CNS stimulation of the trimethadione type. This informed guess is plausible since, in childhood *petit mal* epilepsy, phenobarbital alone usually increases the incidence of seizures. Trimethadione is not depressant in epileptics and shares with caffeine, amphetamine, and other CNS stimulants the known therapeutic effect of reducing the incidence of *petit mal* seizures. This effect was found by Perlstein[9] with meprobamate therapy of childhood *petit mal*.

The published clinical reports[7, 8, 11, 12] appear to favor the use of meprobamate for the treatment of anxiety, alcoholism, and other emotional-behavior states. The use of a drug with combined sedative and stimulant actions is not unique, for a product called Dexamyl, that combines 5 mg. of *d*-amphetamine with 30 mg. of amobarbital, has been prescribed for anxiety states for several years. This combination has also caught the fancy of the anxious, overworked public, but the enthusiasm of the medical profession has been cautiously tempered by the knowledge that the daytime use of barbiturates may lead to overdosage and the characteristic abstinence syndromes of barbiturates, namely, paranoia, psychosis, or *grand mal* seizures. We hope that, in future clinical studies, meprobamate will be carefully compared with Dexamyl, and that it will not be placed in the same class as chlorpromazine or reserpine.

Summary

Meprobamate has been studied to determine its effects on: (1) the conditioned avoidance responses of the rat and monkey; (2) the strychnine and pentylenetetrazol thresholds of the mouse; (3) the spinal reflexes of the cat; and (4) the electroencephalogram of normal human subjects.

Meprobamate produces sedation in both the rat and the monkey. In contrast to chlorpromazine and reserpine, it does not inhibit the conditioned response of the rat in doses up to and including those that produce ataxia and an inability to hold on to a pole. In the monkey, nonataxic doses produce no decrement of the conditioned response.

In the mouse, meprobamate resembles trimethadione in its antagonism to both pentylenetetrazol and strychnine. It resembles phenobarbital in its antipentylenetetrazol activity and, in both tests, its effect is unlike that of mephenesin. Its duration of action is similar to that of phenobarbital.

Forty mg./kg. of meprobamate injected intravenously produces an inhibition of the spinal reflexes of the cat equivalent to that produced by 2.5 mg./kg. of phenobarbital or 20 mg./kg. of mephenesin.

In the normal human subject, meprobamate, in single oral doses of 1600 to 2000 mg., produces a 20 to 30/sec. low-voltage activity in the electroencephalogram during the waking and drowsy states that is not unlike the fast activity produced by secobarbital, phenobarbital, and paraldehyde.

In the light of the results of these tests we have concluded that meprobamate is not an ataractic drug such as chlorpromazine or reserpine, and that it exhibits few of the properties of mephenesin, but that it can be classified as a barbiturate-like drug with some CNS stimulant properties that may simulate those of trimethadione. Perhaps it will be found to resemble more closely a combination of *d*-amphetamine and amobarbital.

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Discussion of the Paper

F. M. Berger (*Wallace Laboratories, New Brunswick, N. J.*): I have no quarrel with Pfeiffer's experiments. I should like to point out only that he interpreted them in a different way than I should have done. He calls chlorpromazine and reserpine ataractics, but he considers drugs such as Phenergan and Sparine (which are very closely related to chlorpromazine) as antihistaminics and anticholinergics. This does not appear justified, as chlorpromazine possesses antihistaminic and anticholinergic properties of a similar order as Phenergan and Sparine. Also, the blocking of the conditioned avoidance re-

sponses is obtainable with Sparine or Phenergan as it is with chlorpromazine. So it is difficult to see the reasons for an artificial separation.

Further, I should like to draw attention to the elevation of the threshold to strychnine after the administration of phenobarbital and mephenesin. In the slides shown by Pfeiffer, these two compounds have a similar slope. Are we to conclude, therefore, that phenobarbital is like mephenesin? I do not think we should. We all know how difficult it is to establish these thresholds. Therefore, with anticonvulsant activity, if we take a criterion of a yes or no response such as "survived" or "died," where there is no room for judgment, we notice that in Pfeiffer's illustration the only two drugs that will protect all animals from death from strychnine would be mephenesin and meprobamate. It is difficult to do so with phenobarbital or trimethadione, even with large doses.

In Pfeiffer's records of the knee jerk, all he showed was the response within 2 min. after injection of the drug. It happens that meprobamate, even if given intravenously, requires 15 to 20 min. to develop its full effect. Therefore it is surprising that Pfeiffer noticed anything at all after 2 min. On the other hand, mephenesin works instantaneously, but most of its effect is gone within 10 min. I agree with Pfeiffer that meprobamate, when evaluated on spinal reflexes, may be a somewhat weaker interneuronal blocking agent than mephenesin. Meprobamate has, however, a much longer duration of action.

As far as brain waves are concerned, we have noticed that it was necessary to give 2 gm. (5 tablets taken in 1 dose) of meprobamate to produce minimal changes that would not be interpreted as significant by all observers. Several electroencephalographers who investigated the effect of meprobamate did not notice any characteristic changes in cortical leads after the normal dose of 1 or 2 tablets. It is, of course, a fact that enough of anything will produce changes.

Lasagna reported that meprobamate, in suitable dosage, will produce sleep. That is correct, but so will morphine, and morphine is not classified as a hypnotic. If it is pain that prevents sleep, and morphine is used to remove the pain, then morphine will produce sleep. If it is anxiety that prevents sleep, and meprobamate is used to remove the anxiety, then meprobamate will produce sleep. That makes neither meprobamate nor morphine a hypnotic.

S. Irwin (*Department of Pharmacology, Schering Corporation, Bloomfield, N. J.*): I should like to say only that, in the dog, meprobamate appears to be a locomotor stimulant.

K. Unna (*University of Illinois College of Medicine, Chicago, Ill.*): As Irwin said, as Pfeiffer has presented here, and as we have found in our test on mice, meprobamate is a locomotor stimulant in dogs. I should like very much to see this fact discussed further, because I believe that these important stimulatory, excitatory effects are important and can be demonstrated in laboratory animals. I do believe these effects have clinical counterparts about which we should like to hear more.

J. G. Miller (*Neuropsychiatric Institute, University of Michigan, Ann Arbor, Mich.*): Locomotor stimulation may be related to some kind of cortical disinhibition, as evidenced in the similar activity of eels and other Apodes. Pfeif-

fer's presentation, our finding of increased sweating during the driving test, and the presentation by Marquis, all might point to the related phenomena as similar measures or indications of the same thing.

G. Chen (*Department of Pharmacology, Parke, Davis & Company, Detroit, Mich.*): In one of our tests for drug classification we used intravenous injection of three convulsants: strychnine, Metrazol, and caffeine. In this simple test, Dilantin was very effective against Metrazol, and was not effective against strychnine or caffeine. Mephenesin was very good against strychnine and Metrazol, but was not too good against caffeine. Barbital was very good against all three convulsants. In agreement with Pfeiffer's observations, we found meprobamate to belong in the last group of compounds.

C. C. Pfeiffer: Berger accuses my associates and me of using large doses in order to get an effect on the electroencephalogram. I read the following quotation from Berger's paper: "A healthy male subject of 31 years took 8 tablets within 1 hour. There were no changes in his electroencephalogram. Thus, it would be incorrect to call meprobamate a hypnotic." We were not brave enough to give 8 tablets (3200 mg.) in a 1-hour period, nor could we agree that the effect of phenobarbital on the raising of the strychnine threshold is impossible. We did, of course, get a complete antidotal effect of strychnine toxicity with phenobarbital.

In regard to the effect on the internuncial neurons, Berger criticizes us for not waiting long enough for the effect of the meprobamate to occur. We rate meprobamate at 20 mg./kg., which is one half the dose that he has cited in his paper in the *Journal of Pharmacology*, namely 40 mg./kg. The time curves in our graphs and his are almost identical. With only one half the dose, we found an effect within the specified time, but we found a greater effect with mephenesin and phenobarbital.

In regard to the conditioned response, it is true that promazine and other drugs, if given in ataxic doses, will inhibit the conditioned response, but the therapeutic index between the specific inhibiting of the conditioned response as with chlorpromazine and reserpine is, I believe, larger than it is if one compares the lethal dose of promazine with the ataxic dose needed to inhibit the conditioned response. Because of this, I continue to maintain that drugs classified as somewhat antischizophrenic or ataractic should probably be somewhat specific in their inhibition of the conditioned response.

Part II. Treatment of Psychoneurotic Conditions

THE EFFECTS OF WARD TENSION ON THE QUALITY AND QUANTITY OF TRANQUILIZER UTILIZATION*

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The greater part of clinical research involved in evaluating tranquilizing drugs has followed traditional patterns of psychological investigation, with emphasis on internal changes in the person receiving medication. These changes have been ascribed primarily to a specific action of the drug on the central nervous system. It has frequently been pointed out,[1, 2] however, that the total field of the many transacting factors within which a drug is prescribed and administered to a psychiatric patient encompasses more than his internal milieu. Many additional variables have significance in the final effect, but these factors have rarely been studied experimentally, except in the so-called double-blind investigations. These variables may be classified under the following two major headings: (1) the psychodynamic implications of drug prescription and utilization; and (2) the social context of drug administration. The first factor focuses on the symbolic meaning to the patient of receiving a drug administered by a significant person. The second factor focuses on the social conditions under which drugs are prescribed. This second factor is the subject of our paper.

A number of social factors are important in the qualitative and quantitative utilization of the tranquilizing drugs in the psychiatric-hospital setting. These include:

(1) *The ideology of the psychiatrists and their concomitant attitudes toward various forms of therapy.* In a previous paper[3] we discussed the adverse effects of negative attitudes toward the use of tranquilizing drugs; this was contrasted with positive results obtained in institutions where psychiatrists had highly enthusiastic attitudes regarding drug effectiveness. Feldman,[4] in discussing this topic, categorized the medical staff at the Topeka State Hospital into 4 groups, according to attitudes regarding drugs. He showed that the more enthusiastic drug evaluators obtained more success with medication than did their less enthusiastic colleagues.

(2) *The quantity and quality of consistently available ward personnel.* Most drug evaluations reflect current shortages in the number of available ward personnel and are conducted in hospitals where this fact limits the range of alternative modes of patient care. Drug results obtained in institutions that possess high personnel-patient ratios tend to differ from those with lower ratios.

(3) *The economic factors.* Donnelly and Zeller[5] have pointed out that, if it is

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necessary to administer a particular drug for 3 months to obtain an adequate clinical trial, patients who cannot afford such a lengthy private hospitalization will be treated by other means.

(4) *The physical construction of the nursing unit, including the number of patients per room, the size of the unit, and the available recreational space.* Relatively isolated patients may respond to drugs quite differently from patients accustomed to living in larger group settings.

(5) *The general level of patient disturbance and the type of patients treated on a nursing unit.* Some nursing units are composed of stable, long-term patients; others are composed of rapidly changing patient groups. In the latter, variations in patient population affect the types of treatment employed. For example, the successive admissions of several manic patients to a single unit affects the treatment of all patients on that unit and, consequently, changes the way drugs are used.

The evidence for the effects of these five factors (and there are probably others) is based essentially on clinical impressions, since few attempts have been made to explore experimentally the significance of the factors in pharmacological or any other form of therapy. The present report is derived from a program of drug research in which we attempted to develop systematic methods for the evaluation of the effects of the social settings of patients for whom a tranquilizing drug had been prescribed. The use of social psychiatric research within the psychiatric hospital is relatively new, the methodological problems involved in developing a practicable experimental design are formidable, and the number of relevant variables is large.

In choosing a variable that reflected significant aspects of the social context of drug administration and could also be operationally defined, we were influenced by recent investigations[6-8] of the therapeutic and antitherapeutic effects of both long-term and transient changes in the social structure of a psychiatric hospital. Our clinical experience corroborated the finding that tension on the nursing unit has wide implications for the patient group, whether the source of tension is in the patients or the personnel. Furthermore, our experience has indicated that the therapeutic measures undertaken when the nursing unit is turbulent differ from those carried out under more usual conditions. We hypothesized that utilization of the tranquilizing drugs would also be modified under different conditions of ward tension. The changes might be quantitative (drugs would be prescribed for more patients during periods of high tension), or qualitative (there might be less concern over potential minor toxic effects under high tension). Alternatively, in the latter case, on certain nursing units one drug might be utilized to relieve tension while, on other units, other drugs might be utilized. Hence, from a wide choice of factors that reflect social conditions on a nursing unit, we chose unit tension as an independent variable to be correlated with a number of indicators of drug utilization.

Method

(1) One of the investigators made a weekly rating of tension on each of the 4 adult units of the Institute for Psychosomatic and Psychiatric Research and

Training, which is the psychiatric section of a 900-bed private general hospital. The large majority of the 80 psychiatric patients were acutely distressed with a wide range of disturbance that was reflected in a gradation of nursing units housing patients according to their degree of disturbance. The patients were treated by a large number of attending and resident psychiatrists who determined the choice of therapy for their individual patients. By and large, it was the attending psychiatrist who decided whether a patient should be prescribed a tranquilizer, and he also chose the specific medication and the dosage schedule.

Weekly tension ratings were made on a 1 to 4 scale, the latter figure reflecting very high turbulence in the patient group, in the personnel, or in both. Each unit had its own independent scale; high turbulence or tension in the open unit was rated relatively low when viewed with the scale for the most disturbed unit, and the ordinary level of tension on the latter unit was rated high on the scale for a less disturbed unit. A rating of 1 indicated that the unit was quiet and relatively undisturbed. When the patients on a unit were considered to be unusually depressed, the rating could become elevated if the nursing personnel were concerned over the lack of activity, or if the depression communicated the presence of tension to the investigator. The ratings were made after a discussion of the week's events on the nursing unit with the personnel. The effect of these events on the personnel and the patients was then evaluated by the investigator in the light of previous experience.

(2) A record was kept of the type and amount of daytime administration of meprobamate, chlorpromazine, promazine, reserpine, and other drugs used in lesser frequency.

(3) Each week every patient receiving one of the above-mentioned drugs was rated by the investigators in consultation with the unit personnel as to whether his behavior was considered improved, unchanged, or worse during that week.

(4) Each month throughout their entire hospital stay the above-rated patients were classified on a 6-point scale (TABLE 1) according to their over-all progress. An attempt was made at these monthly intervals to assess with the attending psychiatrists the role of the drug in the patient's hospital course.

(5) Additional data obtained from nurses, residents, and other personnel were tabulated, which allowed the investigators to keep a flow sheet of significant hospital events that could affect the use of the drugs. This included such topics as current opinions of nursing supervisors about the various tranquilizing drugs, the amount of available personnel, the therapeutic attitudes of the psychiatrists

TABLE 1

RATING SCALE FOR PATIENTS RECEIVING TRANQUILIZING DRUGS

1.	Patient improved; strong evidence that the drug facilitated the improvement.
2.	Patient improved; role of drug not clear.
2A.	Patient improved; strong evidence that the improvement was independent of the drug.
3.	Patient remained about the same.
4.	Patient became worse; role of the drug not clear.
4A.	Patient became worse; strong evidence that deterioration was independent of the drug.
5.	Patient became worse; strong evidence that the drug contributed to the deterioration.
6.	Patient could not be placed in any category.

who treated patients on the project, and the diagnostic categories for each patient.

(6) Additional data included the amount of night-time sedation, the number of transfers from unit to unit, and the amount of seclusion utilized in the hospital.

Results

Chlorpromazine and meprobamate were the only 2 drugs utilized in sufficient amounts for a large number of patients during the 6 months of the study to allow an adequate statistical comparison. When the patients who received meprobamate are compared with those who received chlorpromazine (FIGURE 1), a difference was observed in that chlorpromazine was the drug of choice on the most disturbed closed unit (3N), while meprobamate was used more extensively on the other units. On the least disturbed closed unit (3 E&W) the predominance of meprobamate was more striking, and a χ^2 comparison between this unit and 3N revealed highly significant ($p = <0.01$) differences in the relative numbers of patients on chlorpromazine and meprobamate. In this analysis, 139 patients who received only one tranquilizer during their stay in

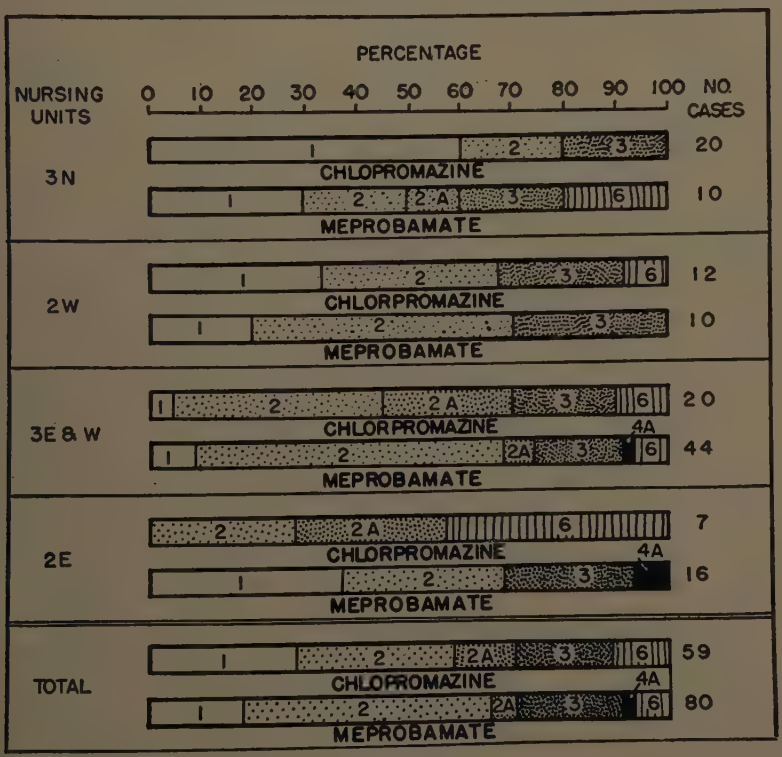

FIGURE 1. Comparison between the results obtained with chlorpromazine and meprobamate. The numbers within the bars refer to the rating scale for patient responses (TABLE 1).

the hospital were included. The total number of patients on tranquilizers (whether on 1 or more) for the 6-months' data analyzed in the present study was 188, approximately one third of the total hospital admissions during that same period.

Utilizing the criteria in TABLE 1, FIGURE 1 also illustrates the effects of chlorpromazine and meprobamate. No significant difference was observed between the 2 drugs on any of the units, although there was a slight tendency for chlorpromazine to be more effective than meprobamate on the most disturbed closed unit. The opposite tendency was present in the open unit.

Correlations between tension on the nursing units and the number of patients on drugs and the amounts of drugs administered during the same week are presented in TABLE 2. There was a tendency ($p \cong 0.10$) to prescribe drugs to more patients who were on the most disturbed unit under conditions of increased tension, but this tendency was related to an increased utilization of chlorpromazine, while the use of meprobamate was relatively constant on this nursing unit. On another unit (2W) a different pattern emerged in that there was a tendency to prescribe meprobamate to more patients under conditions of tension ($p \cong 0.10$) and to decrease the number of patients on chlorpromazine ($p = <0.02$). Correlations between tension and absolute amounts of the drugs prescribed followed the same pattern as the above, but they did not

TABLE 2

CORRELATIONS BETWEEN NURSING-UNIT TENSION AND: (1) THE NUMBER OF PATIENTS ON DRUGS THE SAME WEEK AND (2) THE AMOUNT OF DRUG PRESCRIBED THE SAME WEEK

Variable 1	Dates	Variable 2	Dates	*N*	Nursing unit	*r*	*p*
Tension	12/16–6/22	Total number of patients on all drugs	12/16–6/22	28	3N	0.310	≅0.10
					2W	0.002	N.S.
					3E & W	0.016	N.S.
					2E	0.184	N.S.
					Total	0.263	N.S.
Tension	12/16–6/22	Number of patients on chlorpromazine	12/16–6/22	28	3N	0.326	≅0.10
					2W	−0.446	<0.02
					3E & W	0.091	N.S.
					2E	0.075	N.S.
					Total	0.010	N.S.
Tension	12/16–6/22	Number of patients on meprobamate	12/16–6/22	28	3N	−0.078	N.S.
					2W	0.321	≅0.10
					3E & W	−0.070	N.S.
					2E	0.106	N.S.
					Total	0.211	N.S.
Tension	1/6–6/22	Amount of chlorpromazine prescribed	1/6–6/22	25	3N	0.239	N.S.
					2W	−0.091	N.S.
					3E & W	0.000	N.S.
					2E	0.036	N.S.
					Total	−0.077	N.S.
Tension	1/6–6/22	Amount of meprobamate prescribed	1/6–6/22	25	3N	−0.155	N.S.
					2W	0.352	<0.10
					3E & W	0.001	N.S.
					2E	0.078	N.S.
					Total	0.244	N.S.

TABLE 3

CORRELATIONS BETWEEN NURSING-UNIT TENSION AND: (1) THE NUMBER OF PATIENTS ON DRUGS THE FOLLOWING WEEK AND (2) THE AMOUNT OF DRUG PRESCRIBED THE FOLLOWING WEEK

Variable 1	Dates	Variable 2	Dates	*N*	Nursing unit	*r*	*p*
Tension	12/16–6/22	Total number of patients on all drugs	12/23–6/29	28	3N	0.070	N.S.
					2W	0.058	N.S.
					3E & W	0.014	N.S.
					2E	0.435	<0.05
					Total	1.23	N.S.
Tension	12/16–6/22	Number of patients on chlorpromazine	12/23–6/29	28	3N	0.318	≅0.10
					2W	−0.263	N.S.
					3E & W	−0.278	N.S.
					2E	−0.024	N.S.
					Total	−0.201	N.S.
Tension	12/16–6/22	Number of patients on meprobamate	12/23–6/29	28	3N	−0.510	<0.01
					2W	0.366	<0.10
					3E & W	0.191	N.S.
					2E	0.453	<0.02
					Total	0.249	N.S.
Tension	1/6–6/22	Amount of chlorpromazine prescribed	1/13–6/29	25	3N	0.304	N.S.
					2W	−0.121	N.S.
					3E & W	−0.084	N.S.
					2E	−0.061	N.S.
					Total	−0.138	N.S.
Tension	1/6–6/22	Amount of meprobamate prescribed	1/13–6/29	25	3N	−0.304	N.S.
					2W	0.286	N.S.
					3E & W	0.214	N.S.
					2E	0.328	≅0.10
					Total	0.302	N.S.

achieve the same level of significance. During the first 3 months of the project, highly significant correlations between tension and the absolute amount of chlorpromazine prescribed on 3N were obtained, but the results of the second 3 months and the over-all analysis did not confirm this finding. This reflected the recent tendency of our staff to give more patients on 3N low dosages of chlorpromazine during conditions of high tension.

Comparison of nursing-unit tension and drug utilization during the following week (TABLE 3) showed patterns similar to those discussed above (TABLE 2). On the most disturbed unit there was a tendency to give more patients chlorpromazine ($p \cong 0.10$) and fewer patients meprobamate ($p = <0.01$) during the week following high tension. This contrasted with the open unit, where there was a tendency ($p = <0.02$) to prescribe meprobamate to more patients on the week following high tension. This was also true of the second most disturbed unit ($p = 0.10$).

TABLE 4 illustrates the relationship between the numbers of patients receiving drugs and their quantity to the rating of tension on the following week. On 3N there was a tendency for lower tension to occur in the week following one during which more patients received chlorpromazine ($p = <0.10$) and in greater amounts ($p = <0.05$).

Another finding that tended to separate 3N from the other nursing units is

TABLE 4

CORRELATIONS BETWEEN NURSING-UNIT TENSION AND: (1) THE NUMBER OF PATIENTS ON DRUGS THE PREVIOUS WEEK AND (2) THE AMOUNT OF DRUG PRESCRIBED THE PREVIOUS WEEK

Variable 1	Dates	Variable 2	Dates	*N*	Nursing unit	*r*	*p*
Tension	12/23–6/29	Total number of patients on all drugs	12/16–6/22	28	3N	−0.116	N.S.
					2W	−0.020	N.S.
					3E & W	0.011	N.S.
					2E	0.200	N.S.
					Total	0.249	N.S.
Tension	12/23–6/29	Number of patients on chlorpromazine	12/16–6/22	28	3N	−0.326	≅0.10
					2W	−0.265	N.S.
					3E & W	0.103	N.S.
					2E	0.137	N.S.
					Total	−0.083	N.S.
Tension	12/23–6/29	Number of patients on meprobamate	12/16–6/22	28	3N	0.236	N.S.
					2W	0.166	N.S.
					3E & W	0.080	N.S.
					2E	0.091	N.S.
					Total	0.314	0.10
Tension	1/13–6/29	Amount of chlorpromazine prescribed	1/6–6/22	25	3N	−0.467	<0.05
					2W	0.030	N.S.
					3E & W	0.069	N.S.
					2E	0.142	N.S.
					Total	−0.136	N.S.
Tension	1/13–6/29	Amount of meprobamate prescribed	1/6–6/22	25	3N	0.102	N.S.
					2W	0.007	N.S.
					3E & W	0.001	N.S.
					2E	0.058	N.S.
					Total	0.115	N.S.

illustrated in TABLE 5. There was a highly significant correlation ($p = <0.01$) between dose changes and tension on this unit that was not present on any of the other units. A tendency ($p = <0.10$) toward similar correlation with drug changes (shift from drug to drug or starting new drugs) could also be observed on this unit.

TABLE 5

CORRELATIONS BETWEEN NURSING-UNIT TENSION AND: (1) THE NUMBER OF DRUG CHANGES* THE SAME WEEK AND (2) THE NUMBER OF DOSE CHANGES† THE SAME WEEK

Variable 1	Dates	Variable 2	Dates	*N*	Nursing unit	*r*	*p*
Tension	12/16–6/22	Drug changes*	12/16–6/22	28	3N	0.325	≅0.10
					2W	0.108	N.S.
					3E & W	0.222	N.S.
					2E	−0.286	N.S.
					Total	0.199	N.S.
Tension	12/16–6/22	Dose changes†	12/16–6/22	28	3N	0.533	<0.01
					2W	0.001	N.S.
					3E & W	−0.013	N.S.
					2E	−0.036	N.S.
					Total	0.191	N.S.

* New patients on the drug or a shift to another drug.
† Either raising or lowering the dose.

Under conditions of high tension, focusing attention on a quantitative analysis of drug utilization may obscure qualitative changes. When there is stress within the hospital as a whole or on any of the nursing units, there is a tendency to utilize the tranquilizers in a different manner than under usual conditions. Our method of study has permitted the investigation of all techniques employed in the reduction of high-tension levels on the various units. For example, we have noted the occasions when a unit was rated at the top level of "4," and we attempted to categorize the alternative therapeutic modes utilized on such weeks. These techniques were then compared with those used during ordinary or low tension weeks. The following 2 examples illustrate qualitative changes in drug utilization that we observed when tension was high and demonstrate the interaction of pharmacotherapy with other methods of treatment.

(1) *The shift in the attitude of the staff toward potential toxicity under conditions of high unit tension.* Ordinarily our staff expressed great concern over the toxic effects of the new tranquilizers. This was partly realistic, but the intensity of its concern may have been the reflection of a negative attitude toward pharmacotherapy, especially when minor toxic reactions were involved. The course of one female patient, whose history revealed the presence of an allergic reaction and other untoward manifestations after the previous administration of a large number of tranquilizing and sedative drugs, illustrated the reversal of the ordinary attitudes under stressful conditions on the unit. Because of the allergic history, the personnel attempted to manage this acutely hyperactive psychotic patient by increased attention and personal contact. This was reasonably effective until, after 2 days, several other patients on the unit showed increased disturbance and also required increased attention. At this time the unit staff began to discuss the use of chemical sedation, and the attending psychiatrist responded to this discussion by placing the patient on chlorpromazine and high doses of antihistaminics. The patient responded to this treatment by becoming more controlled, but developed swelling of her ankles. The unanimous opinion on the unit at this time was that the edema was minor, whereas the behavior changes were quite important.

(2) *The increase in intrastaff problems under conditions of high tension and the resultant effects on the utilization of drugs.* Although intrastaff problems occur as part of the day-by-day operation of a psychiatric hospital, internal disagreements may increase when tension is high, and these differences may lead to changes in therapy. This can be illustrated by the case of an adolescent male patient who entered the hospital with a diagnosis of "severe character disorder." He was extremely anxious on admission and, after several days in the hospital, showed increased anxiety, behaving in an extremely provocative manner toward other patients and toward members of the personnel. The attitude of his psychiatrist could be classified at the psychotherapeutic end of the ideological continuum devised by Sharaf and Levinson.[9] This involved a negative attitude toward pharmacotherapy and a tendency to pay little attention to the opinions of the unit personnel regarding a patient. The patient reflected

this attitude when he was placed on low dosages of meprobamate, saying "this stuff is poisoning me." When his behavior became worse, the staff recommended increased sedation, but the attending psychiatrist dismissed this with the comment that the nurses were too anxious. In turn, the personnel responded to this statement with anger, and unit tension rose. Finally the patient became extremely disturbed, threatened to assault several people, and kicked open a door, breaking the lock in the process. This act greatly increased unit tension and, for several hours, both personnel and patients felt markedly insecure. At this point the unit administrator decided to control the patient with chlorpromazine, and 950 mg. were administered parenterally over the course of 4 hours. When the attending psychiatrist came for an interview later that day he noted the patient's staggering gait and expressed concern over the potential harmful effects of chlorpromazine. He recognized the need for medication, however, and an effective compromise was reached when the patient was placed on high doses of meprobamate. The intrastaff tension decreased, and the patient showed an excellent response. In this case the high rating of the unit tension was due to a combination of insecurity due to the broken lock, intrastaff differences regarding therapy, and the presence of an unusually disturbed patient. All of these factors led to a decision contrary to the previous opinion of the patient's doctor.

Discussion

Our investigations have provided preliminary answers to 2 major questions: (1) What do the findings reveal about the use of tranquilizers in our hospital? and (2) What are the implications for the study of the methodology of drug research?

(1) Analysis of the results of our investigations gave some information concerning comparisons between meprobamate and chlorpromazine, a qualitative differentiation of the most disturbed unit (3N) from the other nursing units, and data regarding over-all utilization of tranquilizers in the hospital.

Although a number of other tranquilizers were prescribed, chlorpromazine and meprobamate were the only drugs utilized in sufficient amounts to permit comparative statement. The frequency distribution of their use during the 6-month study (FIGURE 1) indicated the tendency of the attending psychiatrists to prescribe chlorpromazine for patients who were extremely disturbed, and meprobamate for mildly or moderately disturbed patients. The level of agitation and the ability to control self-destructive or assaultive behavior seemed more important than nosological criteria, although our data were not analyzed according to diagnostic categories and subcategories.

Using the scale presented in TABLE 1, analysis of the results did not reveal highly significant differences between chlorpromazine and meprobamate, either in the hospital as a whole or on the nursing units, although on 3N there was a tendency toward better results with chlorpromazine, and on 2W slightly better results were produced by meprobamate.

The scale reflects certain aspects of our attitude toward pharmacotherapy, in that we have included categories involving patients who changed for the

worse after receiving drugs. It is impressive that many evaluative scales are limited to degrees of improvement or, for the worst results, to a category for "no change." Nevertheless, it should be noted that no patient in our series was classified under "5" (which involves strong evidence that the patient was made worse by drugs). The fact that the most common rating was category "2" (indicating that the patient improved, but that the role of the drug was unclear) reflects the difficulty in assessing the basis of improvement in a setting where so many therapeutic procedures are employed. Although we believe that double-blind studies may help isolate the more specific effects of drugs, our major interest lies in the way in which the psychiatric setting and the presence of other therapeutic variables affects drug utilization.

A number of findings pointed toward qualitative differences between the most disturbed unit and the other nursing units. Under ordinary conditions on 3N there was a tendency to rely more heavily on tranquilizers, but this propensity was magnified when the unit was under stress. A significant tendency to increase drug dosage under conditions of high tension emphasized the fact that the tranquilizers served as a safety valve on the most disturbed unit; on other units there was no relationship between dose changes and tension, indicating that, in these settings, other techniques were utilized. The most obvious hypothesis was that retrogressive transfers served this capacity on other units, but our analysis of the data on transfers was inconclusive, as the number of transfers in our hospital was small. Actually, the availability of retrogressive transfer in an emergency might by itself be the important safety valve.

An additional qualitative difference between 3N and the other units could be seen in the tendency to prescribe more chlorpromazine and less meprobamate under conditions of high tension whereas, on the less disturbed units, more meprobamate was used on the week of higher tension ratings. Analysis of the following week's results corroborated this pattern, with chlorpromazine prescription high on 3N the week after high tension, and meprobamate administration high on the other units under these same conditions.

When tension was rated high on 3N there was a tendency to place more patients on chlorpromazine that week and the week following; greater prescription of chlorpromazine tended to lower the tension on the following week. We believe that the study of the nursing units under different conditions added data that might not be observed with more traditional types of analysis. Although in our study the findings showed a quantitative increase of drugs preferred under ordinary conditions, it is conceivable that in certain settings drugs not commonly used may be prescribed under conditions of high tension.

In regard to the over-all use of tranquilizers in our hospital, the study tended to support the assumption that the social environment of the nursing units affected the use of tranquilizers and their prescribed quantity. This implies, of course, that the attending psychiatrist was in some manner responsive to the social context surrounding his patient and himself, and that he modified the treatment program accordingly.

(2) The present study is significantly limited by the fact that its major independent variable, nursing-unit tension, is a very crude measurement. Each point on the scale is composed of heterogeneous phenomena that have not been integrated by precise definition, and the usefulness of the scale in other hospital settings is accordingly quite limited. Furthermore, it was not possible to have an additional independent psychiatric observer make weekly tension ratings. In spite of these limitations, however, we believe that we have learned a great deal from this study regarding the potentialities of such scales, and our confidence in the ratings has increased as the study has progressed. A logical next step involves the breakdown of each level into subcategories to ascertain the relevant factors responsible for changes in drug utilization.

Although the points on the tension scale, as presently constructed, are applicable only to our hospital, it should be noted that the actual tension levels may not be as important as the changes from one level to another. The question "How does therapy vary when the ward is under more stress?" can be asked in any psychiatric setting and may reveal useful information regarding drugs, as well as other therapies. This involves acceptance of the fact that psychiatric hospitals and their component parts are systems that can be studied experimentally and may be compared to each other in a systematic manner. At present the classifications of psychiatric hospitals are gross and descriptive, involving such aspects as size, extent of personnel, and source of funds. It is our opinion that the evaluation of pharmacotherapy (and other psychiatric therapies for inpatients) awaits the development of a scientific approach to the study of the psychiatric hospital as a dynamic system.

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Discussion of the Paper

Question: I was wondering whether there was any consideration of the possibility of doing this sort of study with a third variable, namely, a placebo

that might be compared with these drugs so one might see whether or not the reaction of the patient to the drug caused a return influence on the staff.

M. SABSHIN: I should like to point out that, in previous attempts to do placebo studies in a hospital of this kind, we have had to face the fact that certain social settings are more conducive to placebo than double-blind studies. In a situation where a large number of attending psychiatrists are prescribing medicaments to large numbers, a certain amount of resistance must be expected, not only from the patients, but also from the staff. We hear such statements as, "I don't want my patient to be a guinea pig." We have tried some placebo studies, and it has been my impression that the more active the patient group, the more resistance the group has shown to placebo therapy.

QUESTION: What was the mode of selection, and what kinds of patients were chosen for treatment? Were all the patients treated?

QUESTION: What age groups were involved?

M. SABSHIN: Drugs were given in all the units. They varied to a certain extent, as I have indicated. The study included all patients in the hospital who received tranquilizer medication. Again, I wish to state that this treatment was prescribed by a large number of attending psychiatrists; we simply watched the trends as the various treatments were administered. The age groups of the patients were quite variable, including our youngest, fifteen years of age, up to those in their eighties. Actually, the mean and median were somewhere in the forties.

QUESTION: Relative to the previously mentioned use of placebo, I should like to know whether the reaction was against the drug or whether paranoid reactions were brought out from the point of view of the drug administered. Also, in those patients who reacted to the point of obtaining optimum therapeutic level, was there some effort made to vary the dosage of drugs with the intention of bolstering ego defenses, rather than giving maximum dosage to the point of breaking down these defenses?

M. SABSHIN: All I can say is that those who were varying the doses were not doing so in a systematic manner for testing purposes. On the part of both the staff and the patients, there was a good deal of reflection and concern about toxicity. By and large there was agreement that drugs can be helpful in the repair of ego deficit, but sometimes in practice this attitude found contradiction, so I cannot say whether anything systematic was attempted in terms of bolstering ego defenses. Again, it goes back to the fact that the medications were prescribed independently by the psychiatrist; the investigator had nothing to do with this element of the research.

DIFFERENTIAL EFFECTS OF THE NEW "PSYCHOTROPIC" DRUGS

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Tranquilizing Medication

The action of the new tranquilizing drugs—chlorpromazine and reserpine—as well as that of other phenothiazine derivates related to chlorpromazine, such as mepazine (Pacatal) and promazine (Sparine), is fundamentally different from electroconvulsive therapy in that these drugs appear to suppress the primary, epinephrine-precipitable, subcortical warning or tension anxiety,[1] while exerting only an indirect influence on its secondary disorganizing effects, namely, of panic or depression.

Gliedman, LaSalle, and Gantt[2] found that the tranquilizers reduced or abolished the orienting reflex and thus inhibited the formation of new conditional reflexes. These antiadrenergic drugs probably interfere with the action of serotonin upon the cerebral centers. They achieve their selective effect by specific reduction in the activity of the posterior hypothalamus. The centrencephalic reticular activating system, which mediates arousal, is blocked by small doses of chlorpromazine, but is released by reserpine, as well as by larger doses of chlorpromazine; this release further reinforces the cortical inhibition of the hypothalamus.[3] The resulting suppression of anxiety and its secondary effects are in inverse proportion to the degree to which important ego functions have been disrupted or paralyzed by an excess of anxiety. Hence, tranquilizing medication, particularly with chlorpromazine, is most effective in the manic state since, as I have pointed out elsewhere,[4] that condition is most directly power-driven toward excitation by tension anxiety and is a state in which important ego functions are relatively preserved. Conversely, for exactly the same reasons and in remarkable accord with the fact that inhibitory cortical processes are more readily extinguishable than are excitatory ones,[5] manic psychoses are least readily relieved by electroconvulsive therapy (an extinction type of treatment) unless the treatment is carried to the point of obliterating even the mere perception of warning or tension anxiety.

An ancillary but far from insignificant reason for the superb clinical results of chlorpromazine therapy in manics is that these psychoses tend naturally to be of short duration. If, accordingly, the manifestations of the psychosis can be suppressed for the natural duration of the manic episode, the patient can continue to live a reasonably normal life and may even be able to continue to work without experiencing either the social disadvantages of morbidity or the undesirable suppression of cortical functioning produced by electroshock.

Depression is at the other end of the scale of effectiveness of the new tranquilizing drugs. Not only are chlorpromazine, reserpine, and related drugs entirely ineffective in most cases of depression, but they are actually contraindicated, since they may aggravate the condition. The reason for their ineffectiveness obviously lies in the fact that, in depression, paralysis of the cortical

ego is most profound. Inhibition of ego functions is further aggravated by these drugs for two reasons: (1) the inhibitory state of the ego has not only become independent of continued overstimulation by the warning anxiety that had originally paralyzed the ego into depression, but (2) by a process of negative induction leading to the spread of inhibition, the inhibited state of the ego has extended to include the original warning anxiety, as well.[6] This fact explains the reciprocal relationship between anxiety and depression that stands in contradistinction to the simple vicious-cycle relationship existing between warning anxiety and panic. Thus it comes about that further suppression of the original warning anxiety by means of tranquilizing drugs will actually deepen the existing depression or, in some cases, will precipitate depression. Conversely, enhancing the warning anxiety by epinephrine injection, for instance, may temporarily relieve depression.

Depression is, indeed, the most significant mental-emotional complication arising from the use of these tranquilizing drugs. If administration of chlorpromazine, for instance, is continued too long after control of a manic psychosis (as occurred with 3 patients in my own experience, in whom this drug was administered over periods ranging from 4 to 7 months in an attempt to tone down mild residual hypomanic states), or if reserpine is given to depression-prone individuals for relief of hypertension,[7] depression may be precipitated. This type of depression can be terminated promptly, however, by discontinuance of the drug. Gastrointestinal withdrawal symptoms of chlorpromazine can be covered by Donnatal, the Donnatal then being rapidly withdrawn.

The new tranquilizing drugs are less consistently effective in catatonic and excited schizo-affective states than they are in manic states. In catatonic and hallucinatory paranoid states I have found reserpine relatively more effective than chlorpromazine.

A unique treatment result in my experience is the case of a severe actively hallucinatory psychosis of 5 years' duration in a 43-year-old woman in whom reserpine treatment brought about a state of complete recovery within 5 months. This patient's psychosis had been unresponsive to electroshock therapy (20 treatments) administered 2 years after onset, to insulin coma therapy (60 deep comas) administered 3 years after onset, and to intensive psychotherapy administered throughout these treatment periods and the subsequent intervals. The daily dose of reserpine used in this case was 8 mg. (5 mg. I. M. in A.M., and 3 mg. orally in P.M.) during the first 2 weeks, raised to 13 mg. (10 mg. I. M. in A.M., and 3 mg. orally in P.M.) during the subsequent 6 weeks, then gradually reduced until a maintenance dose of 1 mg. orally in P.M. was reached within the next 3 months. A case strikingly similar from the clinical point of view, of only 3 years' duration in a 39-year-old woman with a history of unresponsiveness to electroshock administered shortly after onset, was treated identically with reserpine. The patient failed to respond in that her improvement fell far short of social, not to say complete, recovery, although the treatments were identical.

The pretreatment Funkenstein test responses in these patients were strikingly different. In the first case (showing favorable response to reserpine treatment) epinephrine-precipitable anxiety had been absent. The amplitude of the blood-

pressure response to epinephrine was within low normal limits in that the blood pressure rose only by 26 mm. Hg in response to 0.025 mg. I. V., and by 58 mm. Hg in response to an injection of 0.05 mg. I. V. There was a moderate but prolonged fall of blood pressure in response to Mecholyl (10 mg. I. M.). While this response fell within the definition of a type-VI response without epinephrine-precipitable anxiety, it was sufficiently close to a type-V response (in view of the merely low borderline adequacy of the response to epinephrine) to suggest the advisability of a systematic investigation of the response of full-blown type-V patients to reserpine therapy. In the second case (showing no significant improvement with reserpine) epinephrine-precipitable anxiety had been present, while the blood pressure rose by 35 mm. Hg in response to an injection of 0.025 mg. of epinephrine. On injection of Mecholyl (10 mg. I. M.), the hypotensive response was slight and unsustained, and the blood pressure returned to the preinjection level for the first time after 5 minutes and again after 13 minutes. This response falls within the definition of type III, with epinephrine-precipitable anxiety.

In most other anxiety and panic states, and in related regressive neurotic and psychotic syndromes, I have found the use of chlorpromazine and reserpine generally unsatisfactory from the long-range point of view, with a few remarkable exceptions that responded very well. All those who did respond well were cases marked by agitation and overactivity, and these are the cases that seem most amenable to chlorpromazine.

A case in point is that of an anxiety-hysteric panic reaction in the case of a 45-year-old male patient whose Funkenstein-test response confirmed the clinical impression that he was free from true depression. A slight undertone of discouragement had suggested the possibility that we might be dealing with a reactive depression with hypochondriasis and hysterical somatization reactions, although true depressive symptoms such as retardation, suicidal throughts, and self-depreciation were entirely absent. Nevertheless, there is a tendency to misdiagnose the condition of such a patient as one of reactive depression, although it is actually an anxiety state, both in terms of psychological dynamics and of the Funkenstein-test response.

The Funkenstein test showed epinephrine-precipitable anxiety in response to an intravenous injection of 0.025 mg. of epinephrine. Injection of Mecholyl (10 mg. I. M.) showed a moderate fall of blood pressure that returned, however, to the preinjection level within 8 minutes. This response falls within the definition of type III, with epinephrine-precipitable anxiety. The Funkenstein test thus confirmed the impression that the outstanding disturbance in this patient was one of anxiety and not of depression, since epinephrine-precipitable anxiety was present, and prolonged excessive response to Mecholyl was absent. This patient was one of the cases of this type who responded well to chlorpromazine.

Reserpine, on the other hand, was useful in some phobic states. All these cases, however, had one thing in common with manic states: the fact that, while the ego boundaries had been breached by panic-anxiety, any secondary paralysis of important ego functions was absent or relatively slight, the clinical

picture being dominated by excitation. As might then be expected, none of the obsessive-compulsives was benefited even temporarily.

The great variation in response to tranquilizing drugs by patients with neurotic and borderline states may in part be explained by the fact that one of the more important effects of these drugs is the enhancement of suggestibility. West[8] has shown that the use of these drugs increases the ease with which patients can be hypnotized or otherwise influenced by suggestion.

LSD (lysergic acid diethylamide), on the other hand, tends to decrease susceptibility to hypnosis and suggestion, although this resistance may be partly attributable to the subjects' anxiety in the novel situation, since suggestibility is somewhat higher on subsequent administrations when the patients are more at home in the situation.

These observations may simplify the explanation of the capacity of tranquilizing drugs to exert a blocking effect upon the model psychoses induced by LSD. The drugs may simply lessen anxiety and enhance suggestibility, and this action may be sufficient to explain their ataractic effect.

Be that as it may, the fact remains that increased suggestibility is one of the effects of tranquilizing drugs. This fact sheds some light on the great variety of therapeutic responses, since the aspect of the drugs' effect that depends upon enhanced suggestibility merely creates a therapeutic potential that must then be utilized by skillful psychotherapeutic management.

Chlorpromazine is useful in relieving states of excitation in the psychoses arising from chronic alcoholism and in states of pathological alcoholic intoxication,[9] as well as in cases of drug addiction, in which it is used to relieve nervous-system excitation released by the withdrawal of narcotics.[10, 11]

Both chlorpromazine and reserpine are useful in senile psychoses. In a case of Alzheimer's disease, with marked agitation, overactivity, and increased talkativeness, a remarkable degree of social improvement was brought about by the administration of chlorpromazine.

Chlorpromazine and reserpine have also been found helpful in the institutional control of chronically disturbed patients in mental hospitals. In the majority of these patients this method of control merely suppresses symptoms without bringing about actual recovery, although physicians who have used large doses of reserpine in such hospital populations of apparently chronic, incurable schizophrenics have consistently reported a social recovery rate of 20 per cent, enabling such patients to return home after many years of hospitalization.

Relaxant Medication

The action of relaxant medication, as exemplified by meprobamate (Miltown),[12] is similar to that of the tranquilizing drugs, except that its inhibitory effect is less profound. This is an advantage in the treatment of psychoneuroses, in which a marked reduction of drive such as that brought about by tranquilizing drugs is often anxiety-provoking and thus tends to counteract the desired effect of the medication. Because of its less profound inhibitory action, meprobamate also does not tend to precipitate or aggravate depression;

but for the same reason it is also much less effective in the treatment of psychotic states of excitement. Its use in the psychoses is limited to the reduction of anxious aftermaths following convulsive electroshock therapy. It is a useful adjunct in the treatment of states of anxiety and angry resentment in the course of alcohol withdrawal treatment (the so-called "dry drunks") in chronic alcoholic patients.[13]

Ataractic (Deconfusing) Medication

This interesting drug action has been described as the characteristic effect of Frenquel.[14] In contrast to the tranquilizing drugs, Frenquel does not depress the activity of the hypothalamus, either clinically or in the electroencephalogram; it counteracts the effects of LSD and of mescaline without inducing sedation, and it restores the resting activity of the electroencephalogram after its disruption in the form of enduring arousal by LSD or mescaline.[3] A particular area of its clinical application lies in the field of acute confusional and hallucinatory states, including delirioid states secondary to physical illnesses.

Antiphobic Medication

This new group of compounds, whose most effective representative is benactyzine (Suavitil, Parasan), was developed and tested by Jacobsen and his coworkers.[15-18]

The action of benactyzine is fundamentally different from that of the tranquilizing drugs, in that it is anticholinergic (while the tranquilizing drugs are antiadrenergic) and that it facilitates rather than suppresses the orienting response and the conditional reflex responses. It improves discrimination and learning as well, in that the animals respond more readily and precisely. In an ingenious series of experiments using both Masserman's[19] technique of conflict-induced behavior (a form of avoidance conditioning), as well as the classical method of conditioning requiring discrimination of signals, Jacobsen and his co-workers[15-18] proved that benactyzine abolished fear, a psychic pain, and the resulting "neurotic" inhibitory avoidance response engendered by stress. The drug seemed to have raised the "pain barrier," thus eliminating fear. It also appeared to have raised the animal's threshold of inhibitory response to conflictful (supramaximal) stimuli that had previously proven inhibitory, thus rendering the animals undaunted by stresses that heretofore had produced inhibitory neurotic states marked by a slowing of responses and by tense and immobile posturing and behavior. The drug also improved the capacity of the animals to respond promptly and effectively and with a high degree of differentiation to conditional stimuli.

Of particular interest and by way of confirmation of the conceptual scheme of the relationship of these phenomena to depression presented elsewhere[6] and quoted above, is the fact that benactyzine has proved itself to be a mild antidepressant in clinical states of depression in human beings, both of the manic-depressive and the involutional type, as I have had the opportunity to observe in a clinical study of this interesting substance. I believe that this

effect can be well explained by the fact that this drug strengthens the ego boundaries (Rado's "pain barrier").[20] Thus, stimulation that breaks in disruptingly upon the ego is attenuated to the point where it no longer proves supramaximal and therefore inhibitory; instead, it is rendered mildly excitatory. Benactyzine medication reduces psychic pain, thus producing what may be termed psychic analgesia, and reduces fear. The fact that benactyzine is also antidepressant is an interesting confirmation of the relationship between fear and depression. This relationship had been recognized on the psychological plane by Rado,[20] and on the neurophysiological plane by Funkenstein,[21] who found that certain physiological disturbances, including the mobilization of epinephrinelike substances, are similar in fear and depression and are in contrast to those engendered by anger and aggressive feelings and behavior.

It remains to be explained, however, why an anticholinergic substance should reduce both fear and depression while antiadrenergic substances generally deepen depression.

It if of interest to note that alcohol, in a certain dosage, has a similar fear-reducing effect—such as His Majesty's rum ration ("the splicing of the main-brace")—as well as an antidepressant action. Both are offset, however, by the ensuing cortical sedation of alcohol, an effect from which benactyzine in appropriate dosage is remarkably free. On the contrary, benactyzine, at the right dosage level, appears to heighten precision of performance. Further clinical studies will shed more light on the uses of this interesting compound, especially in working out appropriate dosage.

So far, my own clinical studies have been limited to doses of 1 to 2 mg., 3 to 4 times daily. Davies[22] reported that ambulatory "patients with endogenous depression in whom agitation is severe are reporting better control of symptoms with doses of 9 to 15 mg. a day; this is also true of patients with marked agitation and depression in a phobic setting. Patients with reactive depression are not relieved." As emphasized above, most so-called reactive depressions are actually anxiety states, both in terms of their psychological dynamics, as well as in terms of their autonomic test responses (Adrenalin-Mecholyl test) and their sedation threshold.[23]

I have recently had an opportunity to see a case involving a state of intoxication in a 21-year-old girl following the deliberate ingestion of 35 mg. of benactyzine with suicidal intent. The dose was taken at 2:00 in the afternoon. One hour and forty-five minutes later the girl walked down a flight of stairs and told a friend about it in a rather offhand fashion, as if she were telling a joke. She later told me that she felt giggly and silly. The only physical symptom at that time was a heaviness in her legs.

Fifteen minutes later, when she arrived at the emergency ward of the hospital, I found her euphoric and mildly ataxic, although able to walk unaided. Her face was flushed; her general condition was somewhat reminiscent of alcoholic intoxication. She treated the whole episode as a joke, often emitting gales of good-natured laughter, quite at variance with her usually somber and serious demeanor.

Neurological examination revealed a slight muscular weakness, of the legs more than of the arms, with only minimal ataxia, and marked hyperpathy with

enhanced startle-pattern response to sensory stimuli, especially to pinprick and to vibrations of the tuning fork. Her sensory discrimination remained excellent. The plantar reflexes were absent, but all tendon and abdominal reflexes were undisturbed. The cranial nerves were undisturbed, and there was no nystagmus. There was no dysarthria. The girl's sensorium was entirely clear; apart from her state of euphoria, her intellectual processes were undisturbed, and she responded promptly and alertly to questions. Orientation and time sense were undisturbed in every way. Her stomach contents, including most of the ingested tablets, were removed by gastric lavage. Subsequently the patient had a good night's sleep. The next morning she relapsed into her former morose and depressed state with suicidal trends.

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Discussion of the Paper

Question: I am intrigued by Alexander's scheme, which indicates that anxiety produces, on the one hand, excitation, and then with supramaximum effect, depression. I do not see how this fits in with the idea of agitated depression, which we so often see in patients. Also, if the drugs depress anxiety-producing stimuli, then the depression produced by the drugs as a side effect could not very well be due to the supramaximal effects. This depression must be due to other factors.

L. Alexander: The question is well taken. I have been asked this by my friends at other times. I do not claim that my observation explains everything. It is a conceptual scheme into which a remarkable number of things fit. The agitated depression lies somewhere in the first schema, at the borderline, a depression that possesses some element of agitation. It is true that the number of electric shocks necessary to relieve agitated depression falls somewhere between the number needed for the simple depressions and for the severe schizophrenic excitements, so that some of the older Germans used to call it a "misch" psychosis. The in-between stage fits in remarkably well where the stimulation is not quite supramaximal, but there is still much agitation about it, so I think it can be included in this schema.

These views also agree with the experience in conditioning. It has been found that the inhibitory response will not be eliminated by mere termination of the supramaximal stimulus. The inhibition does not extinguish itself spontaneously if the source is removed, and I think this is fully in line with Pavlov's findings.

What I like about the schema is that it produces a hypothesis that can be tested. I have in mind certain studies involving a simple technique in humans. If we can prove that depression is a true inhibitory state in the Pavlovian sense, we shall know as much about it as we should if we could show conclusively that it is not.

What I have tried to present is merely a working hypothesis. We have very few hypotheses in psychiatry that lend themselves to experimental testing. I should be very pleased if I could prove it experimentally.

TREATMENT OF ANXIETY STATES WITH MEPROBAMATE*

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In June 1954 a drug, meprobamate (Miltown), was called to my attention as a potentially effective agent for the treatment of the emotionally disturbed. The drug was discovered and studied pharmacologically by Frank M. Berger,[1-3] who was also responsible for developing mephenesin.[4]

Meprobamate is 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate. Pharmacological experiments showed that the drug exerted a selective interneuronal blocking action, as did mephenesin. It relaxed skeletal muscle, but did not affect monosynaptic reflexes, peripheral nerve, or the myoneural junction. Meprobamate was also reported to be longer acting and more reliable in its results; it did not produce the nausea and vomiting that were often concomitants of therapy with mephenesin. Strikingly different from the effects of mephenesin was a pronounced and long-lasting calming effect apparent on all animals studied. Monkeys treated with meprobamate lost their natural fears and hostilities and became friendly and amenable to handling. Interestingly, they did not become "dopey" or indifferent to their surroundings, but remained alert and retained their appetites.[3] Neuropharmacological investigations using electroencephalographic recordings showed a pronounced influence of the drug on subcortical structures, with greatest slowing and synchronizing of potentials from the thalamus.[5, 6] This calming action of the drug interested me in testing its possibilities clinically with patients referred to the Psychiatric Department at the Albany Hospital for evaluation and treatment.

Scope of the Study

The patients studied were seen during the period from September 15, 1954, to July 15, 1956; they had been referred from general practitioners and from medical consultants. The group studied showed varying intensities of anxiety, tension, or "nervousness," either as the only complaint or as important among other complaints. Within the limits of this criterion of selection, all patients who reported during the period of the study were included, regardless of the diagnosis and regardless of whether the illness was acute or chronic. Three hundred and twelve patients were treated with meprobamate during this study.

Procedure

Patients were given a psychiatric evaluation upon referral and were seen at intervals of one week and, later, as often as progress permitted. Psychotherapy in the initial contact was minimal in all cases. Patients who did not show satisfactory results from meprobamate treatment in a reasonable period of time—usually one to two weeks—were transferred to other treatment. However, all patients, whatever the duration of treatment, have been included in the analysis of results.

* The meprobamate (Miltown) used in this study was supplied by Wallace Laboratories, New Brunswick, N. J.

Dosage

The standard dosage used was one 400-mg. tablet 3 times a day. Some patients received an additional tablet at bedtime. In occasional instances the dose was reduced to 1 tablet twice a day or ½ tablet 3 times a day when this appeared adequate as a maintenance dose.

One large group of patients was treated with a combination of sodium amytal and meprobamate. Treatment initially consisted of 65-mg. sodium amytal with 400 mg. of meprobamate 3 times a day. Later, dosage was reduced as progress permitted.

Standards of Evaluation

Two criteria were used in evaluating the results of treatment with meprobamate alone or with meprobamate in conjunction with another drug: (1) the extent of relief from presenting symptoms, and (2) the degree of improvement in social and work adjustment. The following definitions were utilized in assigning final ratings:

Very good improvement—substantial to complete relief of symptoms, with good social and work adjustment.

Good improvement—considerable relief of symptoms, with significant improvement in social and work adjustment.

Some improvement—some relief of symptoms, but no improvement in social or work adjustment.

No improvement—negligible or no response to treatment.

Results

TABLE 1 shows the conditions in which meprobamate was used both alone and in combination, and the results obtained. TABLE 2 shows the results

TABLE 1

RESPONSE OF 312 PSYCHIATRIC PATIENTS TO TREATMENT WITH MEPROBAMATE

Diagnosis	No. cases	Very good	Good	Some	None	Per cent very good or good	Per cent some improvement
Psychoneurosis							
Anxiety state	152	46	74	23	9	79	94
Phobic	6		2	1	3		
Obsessive-compulsive	7	1		4	2		
Conversion reaction	6			2	4		
Other	76	12	32	21	11	58	86
Psychophysiological reaction	21	6	8	4	3		
Personality disorder							
Alcoholic addiction	7	4	2		1		
Barbiturate addiction	2	2					
Manic depressive reaction	9	2	2	4	1		
Schizophrenic reaction	8		2	4	2		
Involutional depression	8		2	3	3		
Various	10	4	2	3	1		
Total	312	77	126	69	40	65	81

TABLE 2
MEPROBAMATE USED ALONE

Diagnosis	No. cases	Very good	Good	Some	None	Per cent very good or good	Per cent some improvement
Psychoneurosis							
Anxiety state	101	26	46	20	9	71.2	90.0
Conversion reaction	6			2	4		
Phobic	4		1	1	2		
Obsessive-compulsive	4	1		2	1		
Other	53	3	26	15	9	54.7	83.0
Psychophysiological reaction							
Personality disorder							
Alcoholic addiction	7	4	2		1		
Barbiturate addiction	2	2					
Manic depressive reaction	9	2	2	4	1		
Schizophrenic reaction	8		2	4	2		
Involutional depression	8		2	3	3		
Various	9	3	2	3	1		
Total	211	41	83	54	33	58.7	84.3

with meprobamate alone. In patients in what were classified as anxiety states, anxiety, "nervousness," and tension were clearly dominant presenting symptoms. The psychoneurotic conditions classified under "other" did not fit into any of the previous categories and presented mixed symptoms, such as anxiety and depression or other neurotic patterns.

The results shown in TABLE 1 indicate that meprobamate has a definite effectiveness in anxiety states. In other disturbed conditions the drug appears to be of value in proportion to the components of anxiety and tension that are present. These results confirm closely the observations of Borrus[7] and Selling.[8] Meprobamate was also of considerable value in the treatment of alcoholism and barbiturate addiction.

The 9 patients with manic-depressive reactions were treated with meprobamate only after depressive symptoms had been eliminated by electroconvulsive therapy. The results reported, therefore, describe the degree to which postelectric shock confusion and tension were relieved. The schizophrenic group consisted of 2 acute paranoid, 2 acute unclassified, and 4 chronic undifferentiated. The 2 cases showing good response consisted of 1 acute paranoid and 1 acute unclassified category. The group listed as "various" consisted of 5 cases of cerebral arteriosclerosis, 2 of posttraumatic encephalopathy, and 3 of postencephalitic parkinsonism. The completely unresponsive case was one of cerebral arteriosclerosis.

The following case illustrates the manner in which symptoms of tension and anxiety were overcome by the use of meprobamate:

A 28-year-old married white female, the wife of a local physician, gave a history of an uneventful adjustment in her marital and social relations until the termination of her second pregnancy. When she arrived home with the baby she began to display evidence of nervousness, irritability, insomnia, and loss of appetite.

Her obstetrician recommended B complex and barbiturate sedation. She could not tolerate the barbiturate and complained bitterly of being "dopey" and sleepy. She also began to fear that her baby would be affected by the drug as a result of breast feeding. As time passed she became increasingly irritable and could not care for her child. At this time she was referred for psychiatric help.

Psychiatric evaluation failed to reveal any significant pathology except for the obvious tension, restlessness, and insomnia. Mere discussion of the various factors contributing to her plight did not alter her symptomatology.

She was started on meprobamate, one 400-mg. tablet 3 times a day, and within 2 weeks she was free of all symptoms of acute tension. She began to sleep soundly. When interviewed 1 month later she was symptom-free and had discontinued medication.

Combined Therapy

Other drugs were used in conjunction with meprobamate in 101 cases. TABLE 3 shows the therapeutic responses obtained after the administration of meprobamate with other drugs, and it compares the results with those obtained after the administration of meprobamate only. Meprobamate was given in combination with sodium amytal in 95 cases (TABLE 4 shows the responses to combined treatment). Meprobamate was used with amphetamine in 6 cases,

TABLE 3

COMPARISON OF MEPROBAMATE USED ALONE AND WITH OTHER DRUGS

Medications used	Cases		Very good	Good	Some	None	Per cent very good or good	Per cent some benefit
	No.	Per cent						
Meprobamate alone	211	67.8	41	83	54	33	58.7	84.3
Meprobamate with sodium amytal	95	30.4	35	40	14	6	78.9	93.6
Meprobamate with other drugs	6	1.8	1	3	1	1	66.6	83.3
Total	312	100.0	77	126	69	40	65.1	87.1

TABLE 4

MEPROBAMATE USED WITH SODIUM AMYTAL

Diagnosis	No. cases	Very good	Good	Some	None	Per cent very good or good	Per cent some improvement
Psychoneurosis							
Anxiety state	51	20	28	3		94.1	100
Phobic	2		1	1			
Obsessive-compulsive	3			2	1		
Conversion reaction							
Other	17	8	3	4	2	64.7	88.2
Psychophysiological reaction	21	6	8	4	3	66.6	85.7
Various	1	1					
Total	95	35	40	14	6	78.9	93.6

resulting in 1 "very good," 3 "good," 1 "some," and 1 "none" in the group of "other" psychoneurosis.

It was interesting to note that, in the course of this study, certain patients who did not respond to either sodium amytal alone or to meprobamate alone showed a striking response to a combination of the two drugs.

Duration of Treatment

Of the 203 cases that showed "good" to "very good" results, 87 per cent were on meprobamate treatment for from 1 week to 3 months (62 from 6 to 30 days, 87 from 31 to 60 days, and 28 from 61 to 90 days). The remaining 26 cases in this group took meprobamate for from 3 to 15 months, most of them being on maintenance doses to sustain improvement achieved earlier.

Side Effects

Of the 312 patients treated with meprobamate, almost one quarter complained of some fatigue. This effect wore off with time in all cases. Twenty-seven patients reported that they were troubled by dizziness that, in all but 7 patients, disappeared when the dosage was reduced. Headache was reported by 9 patients early in the therapy with meprobamate. As the treatment progressed the headaches disappeared. Nausea was reported by 11 patients. It became necessary eventually to transfer these patients to other medication. Skin rash, maculopapular in character, was noted in 3 cases. No other side effects were observed.

Discussion

During recent years a number of excellent drugs have become available for the treatment of the emotionally disturbed. With the exception of meprobamate, those most widely used are either antihistamines or *Rauwolfia* compounds. Both these groups appear to act primarily on the hypothalamic area of the brain, with resultant powerful effects on the autonomic functions.

Chemically, meprobamate is entirely different from either of these two major families of tranquilizing drugs. It exerts its action primarily on the thalamus rather than on the hypothalamus. Therefore it is able to produce therapeutic results without disturbing the delicately adjusted autonomic equilibrium of the body.

This fact is of special importance in treating outpatients who must carry on with their everyday work and activities, and in whom such autonomic side reactions as stuffy nose and diarrhea may be very disturbing. Of even greater importance in outpatient treatment is the low toxicity of meprobamate. While the incidence of agranulocytosis, jaundice, parkinsonism, and depression resulting from the antihistamine and *Rauwolfia* tranquilizers may not be unreasonably high in relation to the total number of patients treated with them, still the possibility of their occurrence makes necessary a constant vigilance that is usually not feasible in outpatient practice. With meprobamate, transient drowsiness and an occasional skin reaction are the worst that can be expected. Therefore meprobamate therapy would seem to be the treatment of choice for this type of patient.

Summary and Conclusions

Meprobamate was administered to 312 patients treated at the Psychiatric Department of Albany Hospital. It showed definite effectiveness in psychoneurotic anxiety states, and it appeared to have a selective action in conditions in which anxiety and tension were prominent factors.

The combination of meprobamate with sodium amytal in certain cases seemed to be of greater value than either drug given alone. A few patients reported drowsiness or dizziness, but the former subsided spontaneously upon continued administration. Three patients developed mild skin rashes. Other side effects were not reported. While meprobamate appears at least as effective as other tranquilizers, it seems to be safer and better tolerated and has the added advantage that it does not affect the autonomic functions of the body.

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Discussion of the Paper

Question: Have you had any experience with those patients whose symptoms are not marked, who do not require hospitalization? What was the effect of meprobamate in these cases?

W. A. Osinski: In cases where the anxiety was of rather recent onset and the patient had some insight into the factors precipitating his anxiety, the response to treatment was good.

MEPROBAMATE, A CLINICAL EVALUATION

By Noah M. Dixon

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The findings and opinions given in this paper are the result of clinical observations on consecutive patients seen in a busy medical practice—patients, of course, in whom physical examinations revealed symptoms that possibly could be helped by meprobamate therapy. No specific clinical controls were established. My experience with meprobamate began in November of 1954. During the subsequent two-year period I personally observed the therapeutic effects of this drug in more than 1100 patients. Approximately two thirds of these were active-duty military personnel and their dependents, and one third were retired military personnel and their families. Prolonged follow-up observations and evaluations were made personally in a majority of these cases.

Pharmacological studies have shown that meprobamate resembles mephenesin in its action on the central nervous system, with a central selective inhibiting effect on the intranuncial circuits. It differs strikingly from mephenesin in that it produces a longer duration of effect. It is more effective after oral administration and is better tolerated than mephenesin. Its low toxicity and its faculty of producing minimal unpleasant side effects are very impressive.

Drowsiness and lassitude were observed in approximately 30 per cent of the patients included in this study; in many of these, this was considered desirable. Dyspeptic symptoms and mild nausea occurred in about 10 per cent. In only one patient was the drug discontinued because of severe gastrointestinal complaints. Three patients developed a benign maculopapular eruption that was easily controlled in each case with antihistamine therapy. No signs of systemic toxicity were observed. Very little tolerance to meprobamate developed, and similar dosages were effective over a prolonged period of time. The dosage utilized ranged from 400 mg. up to 6 gm. daily. Larger dosages were somewhat more effective, but in most cases these larger quantities resulted in dyspepsia and drowsiness. Three patients, taking 15, 25, and 45 tablets, respectively, in suicidal attempts, were personally seen and treated. All 3 gave the same clinical appearance of a deep, stuporous state, exhibiting hyporeflexia, mild pupillary dilatation that responded poorly to light, and unpredictable wanderings of the eyes. All 3 patients responded to painful stimulation, exhibited normal respiration, blood pressure, and pulse, and had adequate oxygen exchange. The symptomatology and physical findings passed easily in 4 to 6 hours and required only physical and caffeine stimulation. Complete physical examinations and laboratory studies revealed no significant abnormalities, and recovery was complete. In reviewing my records and observations I have selected for discussion six categories in which I have found meprobamate a most useful and helpful drug when used in conjunction with the established therapeutic methods and psychotherapy.

Gratifying results were observed in those people complaining of head pain. Tension headaches, those that seemed to occur in relationship to constant or

periodic emotional conflicts or to be caused mainly by sustained contraction of the muscles of the head and neck, showed a strikingly good response to meprobamate therapy. Eighty-six per cent of 104 patients experienced excellent or good results. In most cases suggestive psychotherapy and a discussion of the emotional conflicts were utilized, and this seemed to produce more constant and prolonged improvement. There was no question of the value of suggestion and psychotherapy for these people. Meprobamate was utilized primarily for its tranquilizing and relaxing effects to initiate an early feeling of improvement and co-operation. Interesting manifestations noted by myself and many other observers were the ease and the relaxed manner in which patients under meprobamate therapy could discuss their emotional conflicts. I felt that meprobamate was more effective than the older analgesic sedative combinations, but that it played a role subservient to psychotherapy and to the interest exhibited by a sympathetic physician. Another interesting observation involved seven patients with typical tension headaches who had failed to respond to meprobamate when it was prescribed by another physician. Six of these patients did very well when given the new drug combined with suggestion and a chance to discuss their emotional situation.

In typical migraine and cephalgia attacks meprobamate was of value in only 23 per cent of the cases observed. Vascular headaches were, in general, much less responsive than muscular headaches. Large dosages, up to 3 to 4 gm. of meprobamate daily, were moderately successful in relieving headaches following lumbar puncture, but were of no prophylactic value. The replacement of the removed fluid with normal sterile saline, the maintenance of a prone position for 4 hours after the spinal tap, and the administration of large doses of meprobamate at the first complaint seemed to give the best over-all results in controlling postspinal headaches.

Functional head pain seemed more responsive than organic head pain to meprobamate therapy, although the latter, in most cases, has many functional secondary components that could be favorably affected by the meprobamate-psychotherapy combination. An interesting case was that of a woman with multiple, large, slowly growing osteochondromas of the skull, whose head pain had been corrected previously by surgical extirpation. Subsequently, this woman had a moderate recurrence of the slowly growing lesions and a reappearance of the headaches. She obtained relief with meprobamate therapy.

The treatment of insomnia was entirely dependent upon its cause. Those cases caused by somatic disease and the functional activities of the body, such as urination and defecation, were not within the scope of this paper. The tranquilizing and relaxing effects of meprobamate were found useful in promoting sleep in those troubled by overwork and underactivity. In those persons whose insomnia was related to mental overstimulation, agitation, or excitement, larger dosages of meprobamate were found to be quite effective. The resultant sleep was quiet and reposed, and many patients reported freedom from abnormal tossing, nightmares, and excessive dream states. Chronic insomnia related to functional factor offered quite a problem. A series of 24 patients with chronic anxiety and insomnia were instructed to take 800 mg. of meprobamate instead of their usual barbituric acid derivative at bedtime.

Seventeen of these patients reported good results and continued to request the meprobamate in preference to their original sedative. Military flying personnel frequently relive each mission during sleep. George E. Drury and his associates at Pinecastle Air Force Base, Florida, found that this tendency was markedly reduced by giving meprobamate at bedtime. Sleeplessness induced in personnel who mulled over the day's mistakes, problems, and triumphs, and over tomorrow's challenges and vicissitudes seemed to be remarkably reduced by meprobamate therapy. In the Air Force, preflight sedation and soporific medications are not allowed for the actual flying personnel; hence the problem of attempting to encourage a relaxing rest period with drugs prior to a flying mission has not been investigated. Personal observations revealed that meprobamate was very useful in inducing sleep or a restful period in those people who have difficulty relaxing while in military or commercial aircraft or in other forms of transportation. The rest state induced by meprobamate was found in most cases to be quiet repose, remarkably free from the morning-after depressing effects so frequently seen with barbituric acid derivatives. An interesting case was that of an active-duty officer who stated that he could never sleep while traveling as a passenger on aircraft. Following the oral administration of 800 mg. of meprobamate, he was observed to sleep 4½ continuous hours in a sitting position.

The problem of motion sickness has many centers of significance: the internal labyrinthine canals, the cerebellum, and the vomiting center, with its chemoreceptive trigger zone. Expert opinions range from the belief that all motion sickness is psychogenic to the idea that psychogenic factors play no role at all. According to John C. Mebane and William F. Sheeley of the United States Air Force School of Aviation Medicine, Randolph Air Force Base, San Antonio, Texas, interest in the psychogenic factors of motion sickness is promoted because of the following observations: (1) very tense and unstable individuals are especially prone to develop motion sickness; (2) disagreeable sights and odors increase susceptibility to motion sickness; (3) individuals can be conditioned in the Pavlov sense by previous bouts of motion sickness; (4) the more distraction, the less the tendency to be air sick; (5) in spite of air sickness, fliers can rise to considerable endeavor in times of dire emergencies; (6) placebos have been found to be effective in some cases; and (7) some people are able to control their vomiting so as not to suffer embarrassment.

In consequence of my feeling that psychogenic factors play a large role in motion sickness, during the past two years I have personally screened 29 overly susceptible patients, people in whom the usual drugs such as Bonamine, Merazine, or Dramamine were either only partially successful or actually failed. Eighty-two per cent of these patients exhibited such emotional problems as low motivation, acute situational maladjustment, sense of personal failure, and chronic anxiety and fear. Without purposeful psychotherapy the following program was outlined. Along with the usual antimotion-sickness drugs, doses of 400 mg. of meprobamate were given one hour before flight and again at the time of boarding the aircraft. This same program was repeated a number of times on some of these patients. Although this was by no means an accurately controlled study, the following tabulated results were obtained: 24 per cent

were completely asymptomatic, 62 per cent stated that this program was much better than that with Bonamine or Dramamine alone, and 14 per cent reported no change. In view of the fact that all 29 patients were severely compromised by motion sickness in the absence of meprobamate, these findings seem significant and warrant further investigation. I feel that meprobamate is a valuable product in the therapeutic armamentarium for motion sickness.

Meprobamate is a muscular relaxant that, in massive doses, will produce a flaccid paralysis without respiratory paralysis such as that associated with curare. Furthermore, meprobamate seems to have little or no effect upon smooth-muscle spasm. Its application in conditions of skeletal-muscle spasm and myalgias is very broad, and recently much has been written regarding its usefulness in a wide variety of well-known conditions. It has great value as an adjunct to physiotherapeutic measures, in spastic conditions, and in acute muscular syndromes. Its many advantages over mephenesin have already been related; in my practice, meprobamate has completely replaced mephenesin.

I have observed, as have many others, that meprobamate is of value in the treatment of the acute alcoholic and of the patient experiencing alcoholic withdrawal symptoms. I have found that 800 to 1600 mg. at 2-hour intervals seems to produce the best results.

During the past two years I have treated eight patients with acute active poliomyelitis of the spinal type and have found meprobamate's tranquilizing and skeletal-relaxing effects of great value in promoting the comfort and general sense of well-being in these acutely ill people, particularly during the first few days of their illness. All these patients displayed considerable immediate improvement in their muscle soreness and discomfort; the limited depression of the respiratory mechanism seems to give an adequate margin of safety. Seven of the eight patients considered were adults capable of giving objective and dependable opinions.

All organic disease has a degree of functional overlay, small in some and large in others; in most patients, it is characterized by tension, anxiety, fear, apprehension, and other traits familiar to all of us. I have utilized meprobamate without complication in a wide variety of medical problems as adjunctive therapy to obtain greater relaxation and co-operation in the patient. In many cases the results have been gratifying. Good results were observed particularly in women with the muscle-contracting variety of menstrual pain; in the apprehensive and fearful patient with a recent coronary occlusion; in the withdrawn, irritable, and scratching atopic; in the gasping, bronchospastic patient; and in the tense, driving, ulcer individual. The drug is by no means a panacea. In these problems, meprobamate by itself has but little use; as an adjunct to proved remedies, however, it becomes of value.

In the military service, as in civilian life, states of anxiety and tension are extremely common. The rigors and problems of service life affect most of us at some time in our careers; therefore, the field for therapeutic evaluations is fruitful. Immaturity reactions, particularly those of emotional instability and passive dependency, were observed in forty-nine patients, and all were treated with meprobamate. Seventy-two per cent obtained a satisfactory response with partial relief of the symptoms. The patients seemed to discuss

their fears and problems more easily under the influence of meprobamate, although very few maintained a consistency of improvement without objective discussion and psychotherapy. In the over-all picture, the more severe the problem, the poorer the results. Deep-seated anxiety states in severe psychoneurotic individuals continue to present a serious problem despite all forms of therapy. Some do obtain temporary assistance and partial relief, which lapses rapidly when meprobamate alone is used. Individuals acutely maladjusted to situations who respond unfavorably to newly experienced environmental factors seem to do exceedingly well under therapy. In these cases meprobammate seems to be of great value in tiding the patient over the difficult period. Poorer results are noted if, underlying this maladjustment, there are personality defects or chronic neurotic patterns. Acute superficial fears, apprehensions, and anxiety reactions, common to all of us at some time in our lives, usually respond well to any logical form of therapy, meprobamate included.

This new drug by no means solves all of the above-mentioned functional disabilities. It is as helpful as many, and better than most, drugs but without critical clinical evaluation and psychotherapy it would probably fall by the wayside. With these other measures, however, meprobamate becomes a useful, adjunctive therapeutic drug, one that should be utilized selectively to assist the physician and not be employed in any wholesale attempt to solve his problems. Its comparative freedom from side effects and its mild sedative action enhance its value when applied to such functional problems as have just been discussed.

In summary, let me say that the indiscriminate use of this new agent is, of course, unwise, and that disastrous results can occur because of a lack of proper diagnosis and evaluation. Even allowing for the fact that suggestion, doctor-patient rapport, and other environmental situations influence the response to any medication, I feel that meprobamate is a safe, new tranquilizing relaxant that is moderately dependable and effective in carefully chosen patients. The safety factor and the ease of administration are very much in its favor. Its primary function is as an adjunctive measure to psychotherapy and proved medical therapeutics. I am sometimes reminded of Armand Trousseau's statement, "Let's hurry, hurry—use the new drug before it stops curing."

Discussion of the Paper

R. W. WAGGONER (*Neuropsychiatric Institute, University of Michigan, Ann Arbor, Mich.*): I have been using meprobamate myself for two and one-half years, and when I first started to use it I was very much unimpressed by the benefit I obtained. It seemed to me to be of no value whatsoever. At that time I was very cautious and used unusually small dosages. Since then I have used larger dosages and now I feel that it is a drug of considerable value. It seems to me that, because of the many variables present in the conditions in which this drug seems to be particularly useful, the use of the double-blind technique and the various other procedures that have been described, such as reliance on a placebo, do not have as important a place here as they do with such drugs as antibiotics. I am somewhat concerned about the extreme emphasis occasionally placed upon such procedures. I think we should base

our justification for the use of tranquilizers simply upon whether the drug works all the time or does not work, or whether placebos work as well, or whatever the circumstances may be.

As a note of warning, I should like to relate an experience I had some months ago: a 37-year-old patient came to me stating that he had been very tense and anxious. I thought this was a good opportunity to try meprobamate without the use of any psychotherapy or discussion of the problem. I gave him some of the drug and told him to take 1 tablet 3 times a day. He took the first tablet just before dinner and, within a half hour, had a violent vomiting attack. Apparently this did not frighten him too much, because he took another tablet about 2 hours later and again, within half an hour, had another severe vomiting attack. He continued to take the drug for two days, a severe vomiting attack following each dose until, finally, his wife called me and asked me whether the drug could have any bearing on, first, his vomiting, and second, a peculiar color invqlvement of his lower extremities. His legs had become dark red, and this redness had extended to his waist.

Becoming concerned, I had him admitted immediately to the hospital where he was found to have a generalized rash involving the groin, the buttocks, the popliteal and antecubital spaces, and the axilla, and these affected parts all had minute hemorrhagic areas. The patient's temperature was 99.2° F., pulse 80, respiration 16, blood pressure 110/70 (about 20 to 30 systolic points lower than the usual blood pressure), and hemoglobin 13.6 gm. He had a hematocrit of 40, a sedimentation rate of 20, and a white blood count of 5800 with normal differential. His urinalysis showed a trace of albumin, with 2 to 5 red cells per high-power field. The following day, 2-plus albumin was found, but there had been no increase in red cells.

The patient was placed on Benadryl, and the condition cleared rapidly. As a matter of fact, within 2 days the skin condition had faded considerably, and I was no longer worried about him. To all intents and purposes, a skin test made with the drug was negative, indicating no susceptibility to the drug.

The interesting thing about this case was that, a day after the patient went home, his wife came down with precisely the same condition, with the same skin involvement of the extremities, although she had taken no drug of any kind. However, she had handled the meprobamate in giving it to her husband.

After about two months we decided that it might be worthwhile to see what would happen if he were exposed to the same treatment again. I asked him if we could try another drug, and I gave him a half (200 mg.) tablet of meprobamate. The patient took this at 6:00 P. M., felt well, and was able to eat dinner as usual. At 9:00 o'clock he noticed a pulling sensation and a feeling of tenderness in the thigh muscles. At 9:30 there was marked itching of both thighs. At 9:45 there was a beginning redness of the skin of the thighs and a beginning edema of the skin of the penis, with marked itching of the penis. At 11:00 the patient was frightened by a severe chill and, at 12:00, he suffered severe vomiting with marked retching that lasted for about an hour. After this he slept for an hour, awoke anxious and tense, rose and walked about, smoked several cigarettes, and went back to bed and slept until 6:30 in the morning. At this time there was itching and redness of the thigh, and he felt

uneasy and had a sense of tightness in his chest, but had no further nausea. He was able to eat breakfast without difficulty and, within perhaps thirty-six hours, was apparently all right.

While this has been the only case among my patients to show a skin reaction, I understand that there have been a number of patients now reported who have had some maculopapular eruption. This is the most marked reaction about which I have heard.

This reaction occurs in so small a percentage of instances that I certainly do not think it should deter our use of meprobamate as a therapeutic drug. I do think, however, that we must not use it indiscriminately. Unfortunately, it seems to me that doctors, when they begin using a drug of this sort, whether it is an antibiotic or not, tend to administer it without a careful examination of the patient or, if it is a tranquilizer, to use it whether it should be used or not.

T. R. Robie (*East Orange, N. J.*): A woman took 16 tablets of meprobamate and a very minimal dose of phenobarbital (3 grains) with suicidal intent. She was brought into the hospital in about 2 hours, could very easily be aroused and, in less than 4 hours, had recovered quite adequately. She received no analeptic or other medication whatsoever. It would seem that, with the 3 cases reported by Dixon, meprobamate is certainly one of the safest of the tranquilizers that we have.

G. B. Koelle (*Department of Physiology and Pharmacology, G. S. M., University of Pennsylvania, Philadelphia, Pa.*): I think most of us would be in complete disagreement with the comment minimizing the importance of double blinds and placebos in testing drugs of this class. Certainly it has been dramatically demonstrated that, if there is any class of drugs where the feelings of the patient and of the physician color the results, it is this one.

This fact is well illustrated by the first clinical reports that appeared on benactyzine in the British Medical Journal, in which one paper[1] reported remarkable results in practically all patients when no controls and no placebos were used. The succeeding paper[2] in the same publication described very little in the way of effects, as compared with the placebos, in the patients who had received nontoxic doses.

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H. S. Goldman (*Medford, Mass.*): The question relative to the use of placebos that was raised in one of the previous papers was omitted here, not because of the need to prove the effectiveness of the drug, but rather to ascertain whether it was the form of the drug administered that was causing the reaction in the patient.

I might cite a case of a 76-year-old woman who had nocturnal frequency and complained of aching in the legs and of an inability to walk without difficulty. She was given the drug in tablet form and, after a week's trial of one dosage four times daily she had little or no response and thought she had received no effect from the drug. The drug was then put into a suspension.

Following a week's use of the suspension of meprobamate she stated that she felt remarkably better, slept through the night with no nocturnal frequency, was relieved of her leg aches, and got along very well.

F. M. Berger (*Wallace Laboratories, New Brunswick, N. J.*): I believe Pfeiffer reported earlier on one case of increased motor activity during sleep, and I was interested to hear that Dixon observed the opposite in many of his patients. Other observers have also informed me that meprobamate given at night produces a decrease of motor activity during sleep so that, in the morning, the bed sheets are almost unrumpled.

R. W. Waggoner: Regarding the double-blind testing, I have some doubt about the moral validity of trying medications on patients, and about the use of placebos. As a matter of fact, I teach my students that it is wrong to use placebos, and I think it is. I do not think medication should be used on a patient unless that medication will have, in my opinion, some action. I know we can all be biased and prejudiced, and I do not claim to be any less so than anyone else, but I feel that a medication should have some value, and I shall not subject a patient to weeks or months of discomfort when I can give him some relief from that discomfort by using the medication, even if most of the value of the medication is psychotherapeutic.

ELECTROMYOGRAPHIC STUDIES ON MEPROBAMATE AND THE WORKING, ANXIOUS PATIENT

By Herman A. Dickel, James A. Wood, and Henry H. Dixon
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In the past decade the attention of physicians has been attracted to the ever-increasing number of pharmacological agents useful in alleviating one of the most distressing illnesses of our time: the syndrome of tension, anxiety, and worry. Not only has interest in these drugs continually broadened, but there has been an increasing variety of means of determining their efficacy in benefiting the symptoms for which they are prescribed and taken.

Reports in the literature have for the most part indicated a widespread acceptance of the use of drugs in modern psychiatric therapy. Both Berger[1] and Selling[2] have reported in their earlier papers on the favorable acceptance by both patient and physician of the value of these pharmacological agents in assisting over-all treatment and in producing a "relaxed, easy-to-deal-with state," which improved the psychotherapist's rapport with his patient and which made for better response to "suggestion, hypnosis, free association, and other therapies."

Subsequent published reports have indicated that many of the drugs have demonstrated increasing psychotherapeutic value. Of these many agents, one of the most publicized and widely used has been meprobamate. The literature of the several companies distributing this drug has indicated that it is intended particularly to reduce "tension and anxiety" and quickly to promote "equanimity, release of muscle tension, and return to normal sleep."

Lemere,[3] Hollister,[4] Thimann and Gauthier,[5] Borrus,[6] and we ourselves[7] have all indicated in recent publications the value of this particular drug in bringing about a reduction of muscle tension and of symptoms of which the patient complains. In all this literature there has been little reference to an evaluation of the drug from any aspect other than its symptom-reducing value and, particularly, its ability to induce a state of equanimity and well-being.

For some time we have been of the opinion that too much emphasis is placed on a drug's ability to clear up symptoms of which the patient has complained, and that too little attention has been given to its beneficial effects on the patient's capacity to work, to accept responsibility, and to function in a well-integrated state. It has been our belief that the return of patients to work and to a reasonable ability to live with and handle the stresses of life is a much more useful result of any pharmacological or other therapy, and this achievement has become our goal.

Methods and Procedures

We have long been extremely interested in the office therapy of a group of individuals best described as having the "syndrome of tension, anxiety, fatigue and, occasionally, depression."[8] This group of people so aptly described by Edmund Jacobson[9] as the "neuromuscular hypertensives" has seemingly be-

come one of the most provocative; nevertheless, we feel that they are often handled incorrectly because of the prevalent attitude toward them.

Briefly, we have come to look on the so-called "tension states" as characteristic of a group of individuals who are, by reason of their inherent qualities and training, the finest product of our culture. These individuals possess, not only the physical qualifications, but the fundamental drives and abilities that serve to make them basic leaders. Their ability and equipment predispose them to great accomplishment. With their drive, their interests, and their make-up they often find that their particular environment inflicts unnecessarily severe and emotionally laden restraints. The consequent conflicts, interpret them as one may, result in a large variety of normal physiological reactions aptly covered by the expression "anxiety tension state." All too often these variations in function are interpreted as "functional pathology." Actually, they represent the normal physiological variations that a healthy organism will exhibit in the face of stress. However, the family, society and, perhaps, medicine far too often have tended to interpret these physiological variations as symptoms, as something either to be "held in," "fought with," or "treated and cured." The person with tensions and anxieties soon becomes convinced that he must be treated and, frequently, he feels he cannot work or even survive.

A number of years ago we began to experiment with a variety of techniques in treating large numbers of these people. On the basis of the relative normality of their physical distresses, we discussed with them the origin of their feelings on a physiological basis, showing them how these symptoms compared with the feelings and bodily reactions that such persons as athletes, workmen, and soldiers experience in the face of excitement or danger. In addition, we attempted to impart a philosophy of living that would enable them to understand their feelings and equip them to deal with the physiological evidence of stress. This therapy attempted to enable them to reduce their physiological symptoms to manageable proportions, and to obviate the development of additional disabilities. These ambulatory procedures were designed to keep the vast majority of our patients at work while they acquired added ability to live *with* their symptoms as they learned to understand and handle them. The technique was chiefly a re-educative, reconditioning type of process, probably similar to the methods used by other groups.

Although these procedures were successful in many cases, the need to reverse the symptoms of tension and anxiety remained. For that reason we have been interested in any pharmacological agent that would be a useful adjunct to any psychotherapeutic procedure designed to assist these distressed people in maintaining usefulness during the time they were learning. Only adjunctive drugs were considered.

In using these drugs, we have felt it necessary, not only for the information of the patients, but for our own knowledge, to know how much actual improvement resulted from the use of the various medications employed. For that reason we have utilized various laboratory types of apparatus in order to demonstrate to ourselves and to the patients their response to any one medication.

Such procedures as psychological and co-ordination tests and skin reactions have been tried.

A piece of apparaus that has recently proved of great value to us in this respect is a cathode-ray oscilloscope with a type of photographic attachment that has allowed us not only to show the patients their own responses to medication, but to photograph these responses and record them from time to time. This apparatus consists of electroencephalographic surface electrodes coupled to a Tektronix type 122 preamplifier coupled by coaxial cable to a Dumont cathode-ray oscillograph type 304A. Photo recordings have been obtained by using a Dumont type 302 oscillographic Land camera. By means of this device we have been able to demonstrate easily the neuromuscular tension before, during, and after the use of any drug, and to compare the objective effect of the drug on the patient with his own statement.

After using this type of apparatus for a time we began to realize that we had not only a means of emphasizing any improvement due to the use of these drugs, but also a means of demonstrating to the patients their ability and capacity to perform certain techniques, as will be described.

It is important to realize that these patients were all diagnosed as having typical syndromes of tension, anxiety, worry, fatigue, and/or mild depressiveness. They were free of any disturbing physical illness and were working at a professional or skilled occupation. They desired to be relieved quickly of a chronic distress due entirely to the typical tension state. All of them were seen regularly at least 3 times a week, and all of them were given daily doses of meprobamate, usually from 200 to 2000 mg. or more a day, the average dose usually being 1600 mg. Most of them took the drug for from 6 to 16 days, the average period of administration being about 2 weeks.

Since we saw these people regularly, we were able not only to record their own feelings of improvement and their statements as to the value of the drug, but also to compare our own clinical findings with the more objective electromyographic findings.

Findings

It was interesting to note that probably less than half the individuals taking meprobamate stated that they felt any real relief. This may have been due to the fact that they were working people and that they were expected to be at work irrespective of how they felt. It may have been due to the fact that we did not particularly encourage any improvement on a suggestive or psychotherapeutic basis. Instead, the patients were told that this drug was designed to help them "relax" and that the degree in which they were able to do so would be recorded by objective means. For this reason the results of our clinical evaluation of meprobamate and its effectiveness may have been somewhat distorted. Nevertheless, our records show that less than half of the patients were actually satisfied with the drug, and that a minority of them actually showed any clinical improvement attributable to its use.

A sampling of cases and the findings noted are shown in TABLE 1. Furthermore, FIGURES 1 and 2 show four typical electromyographic tracings illustrating the reduction in patients' tension after treatment with meprobamate.

TABLE 1

SAMPLING OF RESULTS

Patient	Sex	Age	Amount of drug per day	Subjective response	Untoward reactions	Clinical observations	EMG response	Response to other drugs
A. C.	M	17	1600 mg.	Less nervous	None	No change noted	Amplitude and frequency decreased*	No change
R. M.	F	32	1600 mg.	None	Some sleepiness	No change	Decided amplitude and frequency decreased*	Essentially same
J. D.	M	38	1200 mg.	Less nervousness, less weakness, less episodic crying	None	Did seem steadier	Amplitude and frequency decreased*	No change
D. S.	F	31	1200 mg.	None	None	Slightly improved	Amplitude decreased*	No change
R. J.	M	42	1600 mg.	Questionably better	None	No change	Amplitude slightly decreased*	Increase
R. D.	F	24	1600 mg.	Less tense	Sleepiness	Seemed better	Amplitude and frequency decreased*	Increase
W. D.	M	41	1600 mg.	Felt better	None	No change noted	Frequency decreased	No change
R. M.	M	43	1200 mg.	No better	None	No change noted	Little change	No change
E. S.	M	23	1200 mg.	No better	None	No change noted	No change	Essentially same
E. G.	M	23	1800 mg.	Felt better	Sleepiness	Maybe better	Amplitude and frequency decreased*	No change

* The average decrease in voltage was 70 plus or minus 9 μv.

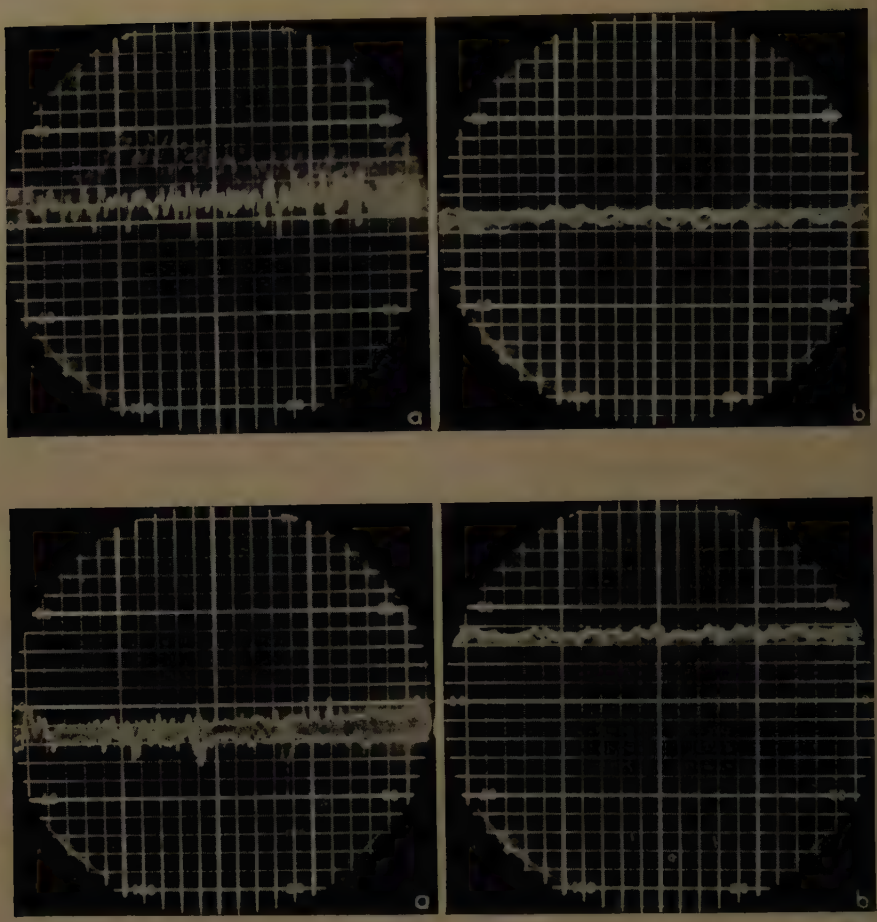

FIGURE 1. Electromyographic tracings of patients (a) before treatment and (b) after treatment with meprobamate.

At first, as might be assumed, we were somewhat discouraged by the results of using this drug, but we soon became aware of a particularly interesting development: irrespective of how these patients felt or whether there was any concrete clinical improvement, the electromyographic tracings of these individuals taking meprobamate showed a very specific improvement in co-ordination and in ability to perform tasks. As shown in TABLE 1, the patients given other drugs showed much less evidence of such improvement.

As they accumulated, these findings furnished an additional means of showing these ambulatory patients that they need not "feel" better in order to do better work. We now had tangible means for showing them that, although there was no change in their *feeling* of tension and anxiety, there was nevertheless a reduction in their tension as recorded on instruments, and an increase in their

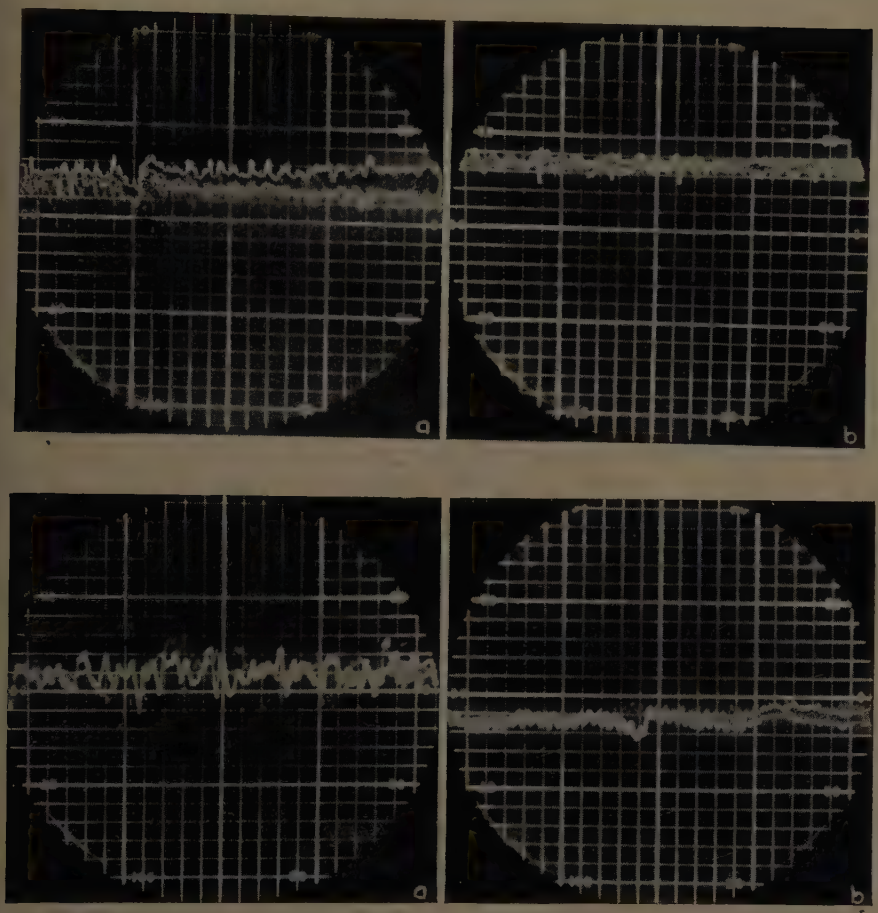

FIGURE 2. Electromyographic tracings of patients (a) before treatment and (b) after treatment with meprobamate.

capacity to co-ordinate and respond to given signals. In so far as their neuromuscular apparatus was concerned, specific improvement in their over-all capacity to perform tasks had actually occurred. This finding proved of tremendous help in reassuring people often too "afraid to work" for fear of impairing their bodily functions.

The results we obtained from applying this information convinced us that it was a tool of a value equal to those supplied by the reports from the patients themselves, by our own clinical observations, and by the ordinary psychological tests.

Discussion

In discussing the effect of meprobamate on tense, anxious, and fatigued working people we recall with interest a suggestion made a number of years

ago by Leo Kanner[10] in defining psychotherapy. We may not quote him exactly but, as we recall, he dealt with the value of "helping the individual make the best use of what assets he had."

We are certain that society's increasing awareness of the problems posed by tensions and anxieties and its demand for the solution of those problems will force an increasing use of pharmacological agents. These will embrace much more than alcohol, the opiates, the bromides, and the barbiturates that have served their purposes in various periods of medical history.

There are a certain number of individuals who can drink regularly and still maintain a fair capacity to work, but the majority will eventually show the ill effects of alcohol. While many of the convulsive disorders have been well controlled with the barbiturates and the bromides, the normal person who takes these drugs to relieve anxiety will often become confused, habituated, or even addicted. The consequences of the indiscriminate use of opiates are well known.

On the basis of past experience we have no reason to doubt that, sooner or later, the currently popular tranquilizing drugs will undergo critical appraisal. Medical articles already describe the habituations, the toxicities, and the adverse reactions following the use of these agents.[11] Eventually sufficient information may accumulate to make us question the value of these "wonder drugs" and medicine may then turn in another direction in search of new and easier means of alleviating tension and anxiety. Allen and MacKinnon[12] have aptly described this trend, and have urged a more realistic attitude.

At the risk of disagreeing with other contributors to this monograph, we believe that we go through these cyclic states of interest in various drugs—first becoming enthusiastic about them, and later pessimistic and discouraged over the results of their use—with consequent misinterpretation of their basic values. As we have indicated in the earlier part of this paper, most of the literature emphasizes the improvement which patients taking these drugs experienced. There is no actual evidence that "feeling better" makes a patient perform or work better. Frequently the opposite is the result. Objective evidence exists to show that, irrespective of how a patient may feel after using at least one of these drugs, his work and his co-ordination may improve greatly, although he himself may not be aware of this change.

If we are to be completely objective and realistic in our psychotherapeutic approach, if we are to help the individual patient achieve a sound and continuously comfortable adjustment to his normal social life, we feel that one objective—perhaps the most important in the psychotherapeutic procedure—should be the patient's speedy return and adjustment to his work. If this is to be accomplished with the assistance of drugs, our attention should be focused not only on the ability of the drug to improve the patient's feeling (for alcohol and the barbiturates do this), but also upon objective proof that the drug improves the individual's capacity to work and accomplish according to his native ability or, as Kanner would say, to see that he is "doing the best with what he has."[10]

Conclusions and Summary

We have attempted to draw no conclusions from our observations noted above. Rather, we have tried to express an opinion in regard to the future evaluation of the tranquilizing drugs, urging the adoption of a broader attitude toward the potential value of these drugs as they affect a patient. This includes not only the normal and necessary evaluation of the effect of the drugs on the individual but also the tangible means that are increasingly available for testing and evaluating the individual's capacity to work more efficiently, to live better socially, and to increase his ability to deal better with his problems and overcome his stresses.

From these preliminary and perhaps not too profound electromyographic studies we have acquired one essential belief: as physicians, we psychiatrists are obligated to adopt improved objective tests for evaluating our therapeutic programs. These tests must be designed not only to determine how much better the patient feels, but also to show whether he has become better adjusted and more effective in his social and industrial relationships.

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Discussion of the Paper

F. M. Berger (*Wallace Laboratories, New Brunswick, N. J.*): Dickel described an objective test that can be used in observing the muscular relaxation that takes place after treatment with meprobamate. A few years ago he investigated mephenesin by a related technique. I should like to hear his comments on the comparative muscle-relaxant effectiveness of these two drugs.

H. A. Dickel: At the time that we worked on mephenesin we did not have available the electromyographic equipment that we have at present. Recently, however, we did some electromyographic tracings on mephenesin and found that its effects did not last over a sufficiently long period. As far as the effect

at the moment was concerned, meprobamate and mephenesin exerted roughly the same effect.

QUESTION: I should like to know the muscles on which these electrodes are placed.

H. A. DICKEL: To a certain extent this depends upon the individual patient. For example, if the patient is a surgeon we should want to show him that the tremble in his hands will be decreased by the medication, and we should place the electrodes over some, if not all, of the muscles in his right or left forearm. The placement of the patient so far as his ability to see the machine will likewise vary. As I pointed out, we are not necessarily trying to add to the scientific information of the medical profession by the use of the electromyogram; we are trying to add to our own and the patient's information. If we wish the patient to see what he is able to do, quite naturally we will place him so that he can see the screen of the oscilloscope.

QUESTION: What is the effect of chlorpromazine and alcohol?

H. A. DICKEL: We do not have enough data to answer this question. Our experience with chlorpromazine in the ambulatory patients has not been as good as it has been with some of the other drugs.

Again, we have been interested in obtaining a drug that would facilitate getting the patient back to work as quickly as possible and keeping him there. Of all the drugs we have used, meprobamate has proved the most effective and has produced the minimum amount of distress.

Part III. Treatment of Psychiatric and Other Conditions with Meprobamate

MEPROBAMATE IN CHRONIC PSYCHIATRIC PATIENTS*

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Meprobamate is a tranquilizing drug that differs from chlorpromazine and reserpine in certain significant respects. First, meprobamate is chemically simple, being a short straight-chain molecule without complex ring structures. Second, in contrast to the marked effects of chlorpromazine and reserpine, it has no effect on the autonomic nervous system. Third, it has several pharmacological effects, pertinent to its effectiveness as a tranquilizer, that differ in kind or degree from those of chlorpromazine or reserpine.

The action of meprobamate on the central nervous system appears to be exerted primarily on subcortical areas, particularly the thalamus. Spontaneous electrical activity of the thalamus of curarized cats treated with the drug showed marked increase in voltage and some slowing in frequency.[1] Meprobamate is also said to block multineuronal reflexes at all levels of the central nervous system, but it has little effect on monosynaptic reflexes, and none on the myoneural junction.[2] It has been suggested that the change in electrical activity of the subcortical centers may be due to release from cortical control through the multineuronal blocking action. However the action of meprobamate on the nervous system may differ from that of chlorpromazine or reserpine, each of these drugs produces a similar type of sedation in animals. In proper doses, meprobamate tranquilizes without producing sleep or motor inco-ordination.[3] This particular type of sedation makes meprobamate clinically important.

A number of clinical studies of meprobamate have already been reported. Favorable results have been obtained in anxiety states and psychosomatic symptoms,[4] in tension states and milder forms of schizophrenic reactions,[5] and in alcoholics.[6] When compared by use of double-blind controls with the *Rauwolfia* compounds, meprobamate was equally effective in treating anxious patients.[7] All reports agree that the conspicuous absence of major and minor side reactions makes meprobamate the drug of choice for the milder group of mental and emotional disorders. The present study reports experience in using the drug in a variety of hospitalized chronic psychiatric patients during the last eighteen months.

Method of Study

One hundred and ninety-one hospitalized chronic psychiatric patients were treated with meprobamate. The variety of psychiatric disorders treated re-

* The meprobamate (Miltown) used for these studies was furnished by Wallace Laboratories, New Brunswick, N. J.

flected the proportion of each in our hospital. One hundred and eleven cases were schizophrenic reactions, 35 were anxiety reactions, 23 were affective disorders, 12 were chronic brain syndromes of various types, and 10 were personality disorders. All except 13 patients were men, whose ages ranged from 20 to 72 years. They had been ill for from 1 to 38 years, the median duration of illness being 10 years. All the patients were treated for a minimum of 2 months, and some had received the drug for as long as 12 months. The majority of patients had been treated for at least 6 months at the time of evaluation. The daily dose of drug varied from 800 to 8000 mg.

The patients with schizophrenic reactions were classified as paranoid in 64 instances, catatonic in 13, hebephrenic in 8, and unclassified or other types in 26. Twenty-eight patients had been ill for more than 12 years. Sixty-one patients had received some form of somatic therapy previously; 5 of them had undergone leukotomies. Eight patients received as much as 4800 mg. of meprobamate daily, while 28 received 2000 mg. or less. The usual daily dose was 2400 or 3200 mg.

The patients with anxiety reactions were a difficult group to treat for the following reasons. First, they had been ill for a long time, the median duration being 11 years. Second, while their symptoms were severe enough to merit hospitalization, the secondary gains of hospitalization tended to prolong them. Third, most of these patients were being compensated for their psychoneuroses. Fourth, 20 of the 35 patients had abused alcohol for a long time. The usual daily dose of meprobamate in these patients varied from 1600 to 3200 mg.

For the purposes of this study, patients included in the classification of affective disorders would not ordinarily come within this category. We did this so that all depressed cases might appear in a single group. The psychiatric diagnoses of the 23 patients in this category were as follows: neurotic-depressive reaction in 7 cases, manic-depressive reaction in 6 (3 manic, 3 depressed), involutional reaction in 5, schizo-affective reaction (depressed) in 4, and psychotic-depressive reaction in 1. Nine patients had required electroconvulsive therapy during a previous depressed episode. The usual dose of drug used was 2400 mg., although the range of dosage was from 1200 to 4800 mg. daily.

Initially, studies using a double-blind control were made to determine the presence of a therapeutic effect from meprobamate. In the first such study, 37 patients were treated with capsules containing either 400 mg. of meprobamate or inert material. One capsule was administered 4 times daily for 5 days, 2 capsules 4 times daily for another 5 days, and 3 capsules 4 times daily for the remainder of a 21-day course. In the second study, 24 patients received successive 21-day courses of either 800 mg. of meprobamate 4 times daily or of placebo. The order of the courses was kept secret. In both studies patients were judged either as improved or unimproved at the end of each therapeutic trial.

Most of these patients continued on treatment with meprobamate following the end of the double-blind trials. Other patients were started directly on the drug because they needed tranquilization and meprobamate seemed to be especially suitable for them. Some of the patients who received meprobamate had been treated earlier with reserpine or chlorpromazine. Others, not re-

sponding adequately to meprobamate, were later treated with one or both of the other drugs.

The criteria for evaluating the treatment of schizophrenic patients were modeled on those used in our earlier studies of reserpine and chlorpromazine. It was hoped that the studies would have enough internal consistency to permit a comparison of the drugs. A rating of slight improvement implied little more than partial sedation of the patient. Moderate improvement indicated either behavioral changes that permitted the patient to participate in activities programs or psychotherapy, or social improvement that permitted the granting of ground privileges or passes from the hospital. Marked improvement meant that the patient had changed greatly according to the above criteria and was being considered for release from the hospital. For evaluating long-term treatment, only moderate or marked improvement was regarded as significant. Improvement to this degree was not considered likely to occur spontaneously, nor had it occurred prior to the addition of the drug to the current treatment of the patient.

Although a similar scale was used for evaluating the other diagnostic groups in this study, obviously different meanings were applied to each. Patients with anxiety reactions were judged on how they felt and how they acted. Because of the particular characteristics of this group of patients, it would be foolhardy to assert that any drug must have a lasting effect; one can only estimate the effect of the drug on the expected immediate course of their illnesses. In patients with affective disorders, relief of the symptoms of anxiety and depression was the basis for judgment. Marked improvement in this group implied that the patient might have required electroconvulsive therapy had he not responded adequately to the drug. Meprobamate was used in patients with personality disorders to curb unpredictable behavior or alcoholism. The goal of treatment in patients with chronic brain syndromes was to control disturbed behavior.

All judgments were made clinically by the patient's psychiatrist, who based the rating not only on his own observations, but also on those reported to him by others in contact with the patient. In most cases the course of illness prior to treatment with meprobamate was well documented for adequate control periods. Ordinarily, the drug was the only new factor introduced into the program of treatment.

Results of Studies

The double-blind studies were useful both for demonstrating a therapeutic action of meprobamate and for indicating the type of patients likely to be helped. The results of the first controlled study are noted in TABLE 1. Two of 15 patients who received placebos improved, while 13 of 22 patients who received meprobamate improved. We interpreted these results as indicating that a definite therapeutic effect was present. The results of the second controlled study are noted in TABLE 2. Once again a therapeutic effect was demonstrated by the greater improvement of patients during administration of active drug as compared with the course on placebo.

TABLE 1

TREATMENT OF 37 PSYCHIATRIC PATIENTS WITH MEPROBAMATE

Progressive doses of 1600 to 4800 mg. daily for 21 days: double-blind control.

Diagnosis	Total No.	No. receiving placebos	No. improved with placebos	No. receiving drug	No. improved with drug
Schizophrenic reaction	27	15	2	12	7
Chronic brain syndrome, senile	2	0	0	2	2
Personality disorder	3	0	0	3	0
Anxiety reaction	4	0	0	4	3
Involutional reaction	1	0	0	1	1
Totals	37	15	2	22	13

TABLE 2

TREATMENT OF 24 PATIENTS WITH MEPROBAMATE (3200 MG.) DAILY OR PLACEBO IN ALTERNATE 21-DAY COURSES: DOUBLE-BLIND CONTROL

Diagnosis	Total No.	No. improved with drug	No. improved with placebo	No. improved with both	No. unimproved
Anxiety reaction	16	9	1	3	3
Schizophrenic reaction	4	1	0	0	3
Neurotic-depressive reaction	2	1	0	0	1
Asthenic reaction	1	0	1	0	0
Involutional reaction	1	0	1	0	0
Totals	24	11	3	3	7

The results of treatment of anxiety reactions were outstanding in both controlled studies, although a strong tendency toward spontaneous improvement was shown in the second study. Treatment of schizophrenic reactions with meprobamate was not so encouraging, but there was little tendency toward spontaneous improvement during the test period. The number of patients in other diagnostic categories was too small to permit any preliminary conclusion to be drawn.

The results of long-term treatment of the entire sample of 191 patients with meprobamate are noted in TABLE 3. Eighty-nine of these patients (46 per cent) demonstrated moderate or marked improvement. Such a frequency of significant improvement following the use of meprobamate would seem to establish it as a potent and therapeutically useful agent.

Forty-four of 111 patients (40 per cent) with schizophrenic reactions were significantly improved by meprobamate. In general, improvement correlated with a short duration of illness and a paranoid type of reaction. The dosage of the drug was of lesser importance. Some patients improved markedly on as little as 1600 mg. daily, while others remained unchanged on doses of 3200 mg. daily. Significant degrees of improvement occurred in 32 per cent of those patients who received less than 2000 mg. daily, as contrasted to 43 per cent of those who received higher doses. The former group was weighted

Table 3

Clinical Results from Treatment of 191 Hospitalized Psychiatric Patients with Meprobamate

Psychiatric diagnosis	No. cases	Improvement noted				Per cent moderate or marked improvement
		Marked	Moderate	Slight	None	
Schizophrenic reaction	111	5	39	41	26	40
Anxiety reaction	35	2	24	7	2	74
Affective disorders	23	8	9	3	3	74
Personality disorders	10	0	1	3	6	10
Chronic brain syndromes	12	1	0	8	3	8
Totals	191	16	73	62	40	46

adversely by the inclusion of some patients who probably received inadequate doses of the drug, such as 800 or 1200 mg. daily. The type of patient with a schizophrenic reaction who responded best to meprobamate was the one whose psychosis was relatively mild, in whom symptoms of anxiety and somatic complaints were prominent. Most of these patients had some insight into their illness. This type of schizophrenic is sometimes made worse by chlorpromazine or reserpine. He reacts with increased anxiety or depression to the strange bodily sensations produced by the autonomic actions of these drugs. The lack of such effects makes meprobamate more easily tolerated by this group.

Few of the exceedingly disturbed schizophrenics were ever treated with the drug, but usually were selected for treatment with chlorpromazine. Those who were greatly disturbed, as well as those with considerable deterioration of behavior, responded less well to the drug. The relative scarcity of marked improvement in this group may be explained in two ways. First, by reason of having milder forms of schizophrenic reactions, this group had less room to show marked change. Second, our psychiatrists have come to expect as a matter of routine that patients will be helped considerably by tranquilizing drugs. They are less likely to make a judgment of marked improvement now than they were two years ago.

Significant improvement was obtained in 26 of 35 (74 per cent) of patients with anxiety reactions. Improvement was manifested mainly by relief of symptoms of inner tension, restlessness, insomnia, and irritability and by a diminution of somatic complaints. Improved co-operation in ward routine, better relations with personnel or other patients, and increased accessibility to psychotherapy were also noted. Some of these patients were able to stay away from alcohol for longer than usual periods, even while absent from the hospital by permission. Ordinarily, hospitalization alone would have been expected to provide some degree of improvement in this group. Unless the betterment exceeded that which could be expected from hospitalization alone, these patients were not regarded as exhibiting significant improvement. Obviously, permanent improvement of such patients is contingent upon factors other than pharmacotherapy.

Significant improvement occurred in 17 of the 23 patients (74 per cent) with

affective disorders. The degree of change was sufficient to be described as "marked" in 8 patients. Only 3 of the patients in this group became candidates for electroconvulsive therapy because of their failure to respond adequately to the drug. Results were uniformly good in patients with neurotic-depressive and manic-depressive reactions, regardless of the phase of the latter psychosis. In looking for possible reasons for the few treatment failures in this group, we were struck by the fact that each patient who failed to respond received no more than 1600 mg. daily of meprobamate. Whether or not increased doses of the drug would have helped these patients is questionable, but it would appear that larger doses should be tried before accepting failure.

In the 12 patients with chronic brain syndromes, the causes were senile or arteriosclerotic brain disease in 5 cases, convulsive disorder in 3, trauma in 2, multiple sclerosis in 1, and Huntington's chorea in 1. Only 1 patient, a disturbed senile woman, showed a dramatic change in behavior. The remainder exhibited either slight changes compatible with increased sedation, or no change at all. The drug had no appreciable effect on the neuromuscular abnormalities of either of the patients with multiple sclerosis or Huntington's chorea, despite the administration of doses as high as 8000 mg. daily to the latter. The choreiform movements in this patient were slightly but definitely relieved by treatment with either reserpine or chlorpromazine.

Only 1 of 10 cases with personality disorders was significantly improved by the drug. These patients often claimed to be deriving much more benefit than objective evidence could confirm.

Comparisons of the results of treatment of the same patient with meprobamate and with either chlorpromazine or reserpine are noted in TABLE 4. In 56 instances in which meprobamate and one of the other tranquilizing drugs were used in the same patients, meprobamate was surpassed in 20, was equal to the others in 17, and was superior in 19 cases. The only group of patients with a sample sufficiently large to be meaningful was that of those with schizophrenic

TABLE 4
MEPROBAMATE COMPARED WITH CHLORPROMAZINE OR RESERPINE IN THE SAME PATIENT

Result	Psychiatric diagnosis				
	Schizophrenic reaction	Anxiety reaction	Affective disorders	Personality disorders	Chronic brain syndromes
Chlorpromazine better	7		1		1
Reserpine better	5			1	1
Meprobamate combined with chlorpromazine better	4				
Chlorpromazine equal	7	2	2		
Reserpine equal	6				
Chlorpromazine worse	5	1	2	1	
Reserpine worse	5		2		1
Both chlorpromazine and reserpine worse	2				
Totals	41	3	7	2	3

reactions. Here the differences between the drugs, as for the whole series, did not significantly favor one or the other. It should be emphasized that these patients were placed on meprobamate because the drug seemed especially suited to their needs. Had the comparison been made between meprobamate and chlorpromazine in patients similarly selected for treatment with the latter drug, the results unquestionally would have favored chlorpromazine. The important point of these comparisons is that there is a group of patients with schizophrenic reactions for whom meprobamate is as helpful as chlorpromazine or reserpine, and that a small but significant number do better on meprobamate than on the other drugs.

Although a close watch was made for complications of meprobamate, few were found, and most of these were due to overdosage. Somnolence, weakness, dizziness and, occasionally, syncope occurred in patients who were started directly on doses of 3200 or 4800 mg. daily. If dosages were increased gradually, these symptoms were less likely to occur. A few patients experienced transient anorexia, nausea, or vomiting. An allergic reaction was noted in 3 patients. One patient had definite urticaria soon after the first doses of the drug. The other 2 patients had itching without urticaria early in the course of treatment. The drug was discontinued in each case, with a prompt subsidence of symptoms. One patient was noted to have a black, hairy tongue that he said was of recent origin. Three patients developed a syndrome of anorexia, nausea and vomiting, marked tremor, restlessness, and mental depression following abrupt discontinuation of the drug. These symptoms occurred when our supply was temporarily exhausted. At least 50 other patients were also deprived of the drug for a brief period at the same time, without having adverse reactions. The rapid appearance of these symptoms after the discontinuance of meprobamate, their character, and their subsidence with the renewal of treatment suggested a possible withdrawal reaction. Since each of these patients had symptoms of comparable type and degree prior to treatment, this syndrome might have represented a rapid recrudescence of symptoms that had been relieved by the drug.

Discussion

Meprobamate has won a place among tranquilizing drugs at our hospital, despite the fact that chlorpromazine and reserpine were well established before its use. At the moment, more patients receive meprobamate than reserpine, although chlorpromazine is by far the favorite. Considering the fact that most of the patients are psychotic—chiefly with schizophrenic reactions—the acceptance of meprobamate has exceeded our original expectations.

Two factors may explain this drug's rapid rise. First and foremost has been the lack of significant toxic reactions. Azacyclonol has been described as having the great advantage of low toxicity and the great disadvantage of having little effect.[8] In the case of meprobamate, low toxicity has been no barrier to beneficial effects. This combination has made the drug highly acceptable both to the patients and to the staff. Second, the drug has filled a few gaps left by chlorpromazine and reserpine in the treatment of psychiatric patients. As

will be discussed below, meprobamate is the drug of choice for psychoneurotics and is fairly effective in patients with depression.

Our initial controlled studies indicated that meprobamate might be fairly effective in patients with psychoneuroses, but considerably less effective in patients with schizophrenic reactions. To some extent these indications were borne out by later studies. Patients with schizophrenic reactions responded better in the later studies primarily because a less severely ill group was treated. Furthermore, these patients had the benefit of a flexible dosage schedule and a longer duration of treatment. A factor that was completely missed in the controlled studies (because we were not looking for it) was the effectiveness of meprobamate in treating patients with depression.

Despite the occasional success with meprobamate in treating a schizophrenic who had not previously responded well to chlorpromazine or reserpine, the latter drugs retain first place in treating this psychosis. The same criteria for evaluating results in the treatment of schizophrenic reactions with tranquilizing drugs have been used in all our studies. To some extent this technique has provided a degree of internal consistency in our studies. Chlorpromazine, which produced significant improvement in 56 per cent of those treated,[9] and reserpine, which produced significant improvement in 54 per cent of those adequately treated,[10] were superior to meprobamate (40 per cent) in such patients. This is true if we assume that each sample of schizophrenics treated was comparable. Actually, the meprobamate-treated group was not as severely ill as the other two groups, accentuating the significance of the difference. What is most important, however, is that meprobamate should be considered for the treatment of some patients with schizophrenic reactions, and that no schizophrenic patient be considered as refractory to drug therapy without having had an adequate course of this drug.

Meprobamate appears to be as effective as any drug in the treatment of patients with anxiety reactions. When one also considers the annoying side reactions from the autonomic effects of chlorpromazine and reserpine, little justification can be found for their use in such patients unless meprobamate has first been tried without success. Sometimes patients experience a euphoric effect from meprobramate, in contrast to the depression often produced by the other drugs. One of the first of our alcoholics treated with meprobamate volunteered: "This stuff makes me feel like I've been trying for the last five years to feel with whiskey." Other patients have offered similar descriptions of their change of mood. Unfortunately, alcoholic beverages offer other satisfactions not provided by meprobamate, so that their use is not long forsworn.

In depressed patients of all types, meprobamate has been helpful to a gratifying degree. This drug is more consistent than the others in providing benefit without the added risk of aggravating the situation. In severe depressions, electroconvulsive therapy still must be used. Except in emergent situations, usually a brief intensive course of mepromate should be tried prior to using electroconvulsive therapy. Failures of the drug in depressed patients in this study appear to have occurred only when an inadequate dose was given. If electroconvulsive therapy is required, the mild anticonvulsant effect[11] and

muscle-relaxant effect of the drug should, if anything, facilitate this form of therapy.

Treatment of patients with chronic brain syndromes of various causes has been no more effective with meprobamate and perhaps not as effective as with the other drugs. We tend to favor use of the drug in patients with behavioral changes accompanying convulsive disorders, chiefly because of its anticonvulsant effect. While the results in this group are no better with meprobamate than with reserpine or chlorpromazine, the latter drugs tend to produce or aggravate convulsions when given in high doses. No drug we have tried has helped appreciably in treating the behavioral symptoms of patients with personality disorders. Meprobamate is no exception.

From the beginning we have felt that tranquilizing drugs affect only the symptoms and not the causes of emotional illness. No pill yet developed can resolve a conflict or remove a stressful environment, much as we might desire it. Accordingly, it has been our practice to use every other feasible form of therapy along with the drugs. All our results, including those reported here, have been achieved by a total-treatment program. To be sure, many patients did not respond to such therapy until the drugs were added. To us this fact indicates that at least partial symptomatic control is a prerequisite for fruitful psychotherapy or psychiatric rehabilitation.

Some observers have made much of the fact that both chlorpromazine and reserpine have strong pharmacological effects on subcortical centers and the autonomic nervous system. The implication has been that the drugs act specifically on some disordered neurophysiological mechanism of schizophrenia. Such reasoning has led to the introduction of the term "chemotherapy" as applied to the use of tranquilizing drugs in mental illness. From the time of Paul Ehrlich, "chemotherapy" has meant the use of a drug to destroy invading parasites or microorganisms in the host. Unless one truly believes in the existence of a "schizococcus," the proper term for this treatment should be "pharmacotherapy." Even this term should not imply too specific an action. Experience with meprobamate now proves that a drug can be effective in psychoses without affecting the autonomic nervous system. Both the sites of action within the central nervous system and the types of effects produced differ appreciably among meprobamate, chlorpromazine, and reserpine. In the light of our present knowledge, the fact that a drug has sedative action, regardless of the neuropharmacological method by which it is obtained, seems to be the best indication that it might ameliorate the behavioral symptoms of emotional illness.

Summary

Meprobamate is a tranquilizing drug of definite usefulness. Qualitatively, the type of sedation achieved resembles, to a much lesser degree, that produced by chlorpromazine or reserpine. The drug causes few toxic effects or noxious side reactions.

Initial studies using a double-blind control indicated the therapeutic effectiveness of meprobamate in psychiatric patients. Further use of the drug re-

sulted in significant improvement in 89 of 191 (46 per cent) hospitalized chronic psychiatric patients. The results of treatment of schizophrenics were not as good as we have obtained from chlorpromazine or reserpine, although occasional patients improved more on meprobamate. The results from treating patients with anxiety reactions or affective disorders were quite gratifying. In these patients meprobamate appears to be the drug of choice. Treatment of chronic brain syndromes and personality disorders was less than satisfactory.

Meprobamate has been surprisingly well received both by the psychiatric staff and the patients of our hospital. The paucity of toxic and side reactions accounts for much of this popularity. In addition, meprobamate fills a few gaps left by the other drugs. Any psychiatric patient who has not responded adequately to either or both of the other major tranquilizing drugs should be given a course of meprobamate before being regarded as refractory to pharmacotherapy.

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Discussion of the Paper

N. S. Kline (*Rockland State Hospital, Orangeburg, N. Y.*): My associates and I tried meprobamate on three separate groups of chronic schizophrenics and found that there was no ataractic effect. There was a mild sedative effect in some of the patients. I think, essentially, that this is not too different from what Hollister said.

Part of our difficulty lies in the fact that we are really dealing with at least two classes of drugs under the name of tranquilizers. One of these is what we might call a psychic relaxant (sedative) and the other an ataractic. There are certain patients, including schizophrenics, in whom the psychic relaxation

brings about a symptomatic improvement. Other patients, more seriously disturbed, require a more severe type of treatment. For the present, at least, the drugs used in this latter case can be called ataractics. Essentially, I think Hollister's results are those caused by a psychic relaxant rather than an ataractic, and the only point of real disagreement I have with him is that, in the chronic schizophrenics, I do not see that it would be necessary to try meprobamate if chlorpromazine and reserpine have both failed. In view of the quite negative results in the chronically disturbed patients, the chances of improvement are extremely small.

L. Hollister: We certainly do not recommend meprobamate for the chronically disturbed, deteriorated schizophrenics. I thought I made that clear. We are talking about the much milder case with chronic anxiety—the patient whose social adjustment occasionally deteriorates to the point where he must enter the hospital for a recovery period. In these patients we found that the other drugs often tend to increase the anxiety. Such paradoxical reactions tend to occur in groups of patients closer to normal than are the chronic deteriorated schizophrenics. We found that, in normal people, chlorpromazine and reserpine caused a rather striking degree of depression. In fact, there are many reports of reserpine-precipitated psychosis, and of some also caused by chlorpromazine.

Regarding the difference between ataractic, sedative, and tranquilizing effects, I must confess that I am quite confused. I think we are in a semantic blind, where a new word has been invented for old things. It is true that there is a difference in the type of sedation afforded by the new drugs, but I think it fallacious to imply that we can make a division of pharmacological agents on the basis of whether or not they relieve a particular disease. If it is true that a drugs must relieve schizophrenia to be classified as an ataractic agent, I know of no precedent in medicine by which drugs are classified in this fashion. Furthermore, we are speaking of relieving a syndrome whose causes and borders are unknown. So I cannot get too excited about trying to understand the difference between tranquilizing or ataractic effects, plain old sedations, or the newly coined term, psychic relaxation.

Question: I think it has been noted that, in ill individuals with severe psychoses, chlorpromazine and reserpine will achieve remission rapidly. I should like to know about the ability of meprobamate to bring about remission in some of the acute psychotics.

L. Hollister: I think that we have a much better chance of obtaining a remission in acute psychoses by using any of these three major drugs. Meprobamate is effective in some cases, although our choice has usually been one of the other drugs for these particular patients.

Question: Is there any curve that tells how long the drug must be used before the optimal result can be achieved? Could we say that the longer the patient is ill the longer this takes?

L. Hollister: There is no question about the fact that the duration of the illness is important. The longer the patient has been schizophrenic the less

chance there is for help with any drug although, surprisingly enough, we have seen some patients who have been ill for as long as thirty years gain considerable help from chlorpromazine or reserpine. We have not seen the same response with meprobamate. As far as the period of treatment is concerned, I do not know the answer because, surprisingly, patients differ in the time required for response. I think that if a patient does not respond quickly to the treatment he is receiving, another treatment should be sought. We should require that our patients show some early change before we ascribe any evidence of progress to the drug being used.

MEPROBAMATE IN SENILE PSYCHOSIS

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Introduction

Meprobamate was used at the McLean Hospital in the treatment of a small series of patients with senile psychosis who had various symptoms and presented a variety of problems of management. During the course of the study it was thought necessary to review the nature of some of these problems of caring for the patients, as well as the relationship between the methods of management and the attitudes of the nurses in the creation and perpetuation of the problems found. It did not seem possible, for example, to consider excitement or inability to eat aside from the environment and care of the patients. The methodology of the investigation became almost as interesting as the study of the effect of the drug, since it was necessary to view the drug reactions in the framework of a study of the nurses' relationships with the patients. It was found that the nurses' attitudes toward senile patients had an effect, not only upon their way of dealing with their charges, but also upon their interpretation of the patients' behavior; during the course of this study, the nurses' thoughts about the patients were likely to change considerably, apparently as a result of focusing attention upon the problem and of changes in the patients. It was thought necessary to give special attention to the nurses directly in charge of patients because it is from these nurses that the patients receive the understanding and care upon which they depend for their well-being.

General Problems of Management of Senile Patients

In dealing with patients with senile psychosis it soon becomes apparent that one is much involved in the problems of primitive activities: those of eating, bowel function, and unrestrained hostility. The patients are likely to be unable to feed themselves, or to forget that they started to feed themselves, or to fight help with feeding themselves. Incontinence is often encountered. Sleeping poses a problem because of the patients' tendency to be restless and to wander at night.

Resistance, destruction behavior, and fighting occur and are likely to be of major concern to nurses. Environmental rearrangement and study of each patient's wishes and frustrations are likely to have a considerable effect in altering these problems.

Some nurses feel that not enough is being done for patients unless some semblance of social behavior is maintained by the patients. They often like to have patients in a living room and take special note of what patients have to do with one another. Little interaction usually occurs between two senile patients put together, since there is too little responsiveness to what each has to offer the other. The outstanding exception to this rule is the frequent oc-

currence of hostility to each other. Instead, the devotion of the nurses is sought after by most patients.

A number of patterns of integrated purposeful behavior are retained in all but the most demented patients. These patterns, as they reappear from time to time, may be overlooked by the nurses and, where the patterns interfere with routine care, they may become the focus of troublesome behavior.

Some Special Characteristics of Patients with Senile Psychosis

Disorientation, loss of memory, and general loss of intellectual powers dominate the scene in the care of groups of patients with senile psychosis. Noting the considerable loss of integrated activities, the personnel caring for the patients are likely to overlook the fact that certain personality patterns have been retained. Affects are likely to persist for a long time in spite of the fact that the memory of the event producing the affect may be lost within a few seconds.

It must be remembered that each patient usually responds in his own traditional fashion to the general pattern of his surroundings, and to the things that happen to him. Food seems to be enjoyed just as much by demented patients as it is by persons with intellects capable of comprehending the enjoyment. Patients like pleasant and cheerful surroundings, respond to dignified treatment, reflect uncertainty in the nurses, and react with hostility to hostility.

Even though demented, the patient may retain important aspects of his personality. He may show reactions of frustration when these personality patterns meet with interference. The patient tends to preserve patterns of behavior that are important to him more than he does those that are less important (a paradox is created when intellectual activity itself has been the special life work of a patient). Since the patient is unable to summon intellectual abilities to find a solution to his problem when frustrated, the burden falls upon the nurse or physician to supply the needed problem-solving ability. Personnel who lack empathy often miss the significance of the problem the patient needs to have solved and may aggravate the situation by taking a stand that appears on the surface to be one of supplying reasonable care but produces hostility and resistance in the patient.

Observations Upon the Care of and the Attitudes Toward Senile Patients

The degree to which variations in environment and management can influence the general behavior of patients with senile psychosis has been noted at the McLean Hospital, and it needs to be taken into account in any attempt to evaluate a new agent of treatment. Different residence halls with their different atmospheres and methods produce widely divergent types of behavior in patients. One hall could be characterized as quiet, well appointed, dignified, and staffed by mature nurses, who were deeply schooled in traditions of propriety, respect, and the forthright use of authority. In this hall nearly all senile patients gave the appearance of genteel, quiet, well-dressed old ladies. They showed little anger, responded politely, exhibited little initiative, sought

little attention, and were seldom incontinent. By contrast, another hall with similar patients was staffed by one or two graduate nurses and a number of bustling student nurses, with a variable deportment. This latter hall was poorly appointed; the patients were usually dressed in utility clothes and were fed from trays. They frequently were noisy, tore their clothes, resisted feeding, fought each other, and were often incontinent, but they showed a liveliness not seen in the first hall described. The introduction into this hall of a well-trained and interested head nurse, together with redecoration, resulted in an improvement of dress and feeding, a little improvement in incontinence, and a great increase in talkativeness to the staff.

The nurses' attitudes, ideas, and feelings about senile patients could be expected to influence their behavior toward their cases. A study of problems of this nature has been in progress for several years at the McLean Hospital, primarily through a system of interviewing student nurses. The foremost attitude of the majority of student nurses is that of reversing the situation as to age, of putting the patient into the role of the child, while the nurse assumes the role of the mother. The nurses often like the patients because they find them "cute," appreciative, and lovable. The patients' lack of intellectual capacities contributes to the nurses' tendency to regard them as objects over whom they can exert affectionate authority. They mention their pleasure in seeing the old people cleaned up and tidy. A corollary but not useful attitude is the less prevalent tendency of nurses to see senile patients as "nothings" or to find them distasteful because of their degenerative aspects. Sometimes a student nurse harbors an impersonal attitude, a preference for caring for seniles (in contrast to younger psychiatric patients) because they are "really sick" and because caring for them is "real nursing." Sometimes there is present an overly sympathetic attitude in which the nurse identifies herself with the patient and resents the supposed mistreatment, neglect, and rejection of the patient by his family and by society in general. Some nurses cling to the same expectations that they have for patients with functional psychosis, looking for "something new" from the patient, such as singing, reading, handicraft, or a new social relationship. In some cases this attitude results in the discovery of old activities that can be revived, but often the nurse is disappointed. Occasionally nurses miss the whole point of the dementing nature of senile psychosis and try to stimulate the patient to the development of handicrafts beyond his capability.

The above attitudes are likely to produce a lack of empathy in the imperceptive or the inexperienced nurse. Disregarding dementia, nurses sometimes concentrate upon efforts to overcome the difficulties of the unreasonable behavior of patients. On the other hand, nurses with experience and aptitude are often able to see through difficult management problems. An important element of this study has been the extent to which a drug can change conditions to a degree where some of these problems, seemingly insolvable, can be solved at least in part.

Possible Benefits of a Sedative Drug

In accordance with current knowledge one would expect to obtain only limited benefits to senile psychosis from any sedative drug. One would not expect any basic increase of intellectual power in the patients. In spite of this, general improvement of condition may bring about changes that result in better functioning of the remaining intellect. Decrease in alertness with added clouding of the intellect is an adverse effect found with some sedatives and limiting their usefulness. Improved sleep is an outstanding effect to be expected, although excessive daytime dozing is an undesirable effect. Quieting of certain tensions sufficiently to avoid extremes of emotional reaction in order to give opportunity for better ways of handling behavior has been the means by which the newer sedatives used in psychiatry are generally thought to act. A general change of direction of interest of the patient conceivably could be an effect of a sedative. Also an alteration of the general form of mental activity is a possibility, as has been thought to occur by some in the case of reserpine used to treat schizophrenia.

Observations

In the treatment of 20 senile patients with meprobamate in doses ranging from 400 to 3200 mg. per day, an evaluation of the opinions of the nurses as to the over-all effects gave the following results: 3 patients showed marked improvement; 8 showed moderate improvement; 7 showed minimal improvement; and 2 showed none.

The results were also broken down into different categories by tabulating the influence of the drug upon various symptoms and problems of management. There was benefit to 7 out of 10 patients who needed help in minimizing resistiveness to care. Six of 7 patients suffering from sleeplessness showed improvement. Of 7 patients having problems of an aggressive and destructive nature, such as slapping other patients, pounding at objects, and tearing clothing, 4 were helped. The problem of wandering was serious in 4 patients; 3 were benefited. Of 4 patients who, because of weakness and a tendency to fall, were in restraint some of the time and who struggled against it, 4 were helped to be more quiet.

Several patients showed changes in ways not easily demonstrated by tabulations.

Case I: marked improvement. A 78-year-old woman who had shown progressive symptoms of dementia for 4 years was admitted to the hospital October 21, 1955. She presented problems of screaming, of fighting care, of resisting dressing and undressing, and of fighting going to the toilet. She showed loss of memory and disorientation, was weak, could not walk without help, and was incontinent. She ate well and without much resistance. Except for her resistiveness and shouting, she led a nearly vegetative existence.

Her past history revealed that she came from a wealthy family and that she had married well. She was a social leader, but was not known to be very sociable except when involved in activities of prestige. She always strove "to do things right" and pressed problems to a solution.

When her illness started at the age of 74, she showed not only impairment of memory, but also indecisiveness and what was called a "bathroom complex." She talked of the importance of moving the bowels after breakfast and spent much time sitting at stool. As the illness progressed she was once found working on a child's puzzle. Shortly afterward she became depressed, said "I'm no good" and, after another brief period, became disoriented.

After 3 months of hospitalization the administration of 400 mg. of meprobamate twice daily was started and, shortly afterward, this dosage was increased to 800 mg. Within a few days she became quieter and more co-operative. Then the nurses were surprised to find that she was not only co-operative, but was capable of washing her own face and hands, of sitting on the commode on schedule, of combing her own hair, and of helping to dress herself. She was similarly co-operative about the activities involved in going to bed at night. Although these activities required a considerable degree of purposeful integrated behavior, the patient led a life that was otherwise nearly vegetative; she remained disoriented and exhibited only a brief memory span for recent events. To test the source of the improvement, meprobamate was withdrawn seven months later. The night following its cessation she became incontinent and, a day later, was again resistive, screaming, and not participating in her own self care. After one week, meprobamate was reinstituted in the same dosage, and the original improvement was restored.

Case II: marked improvement. A 71-year-old woman was admitted to the McLean Hospital May 3, 1956. She had been telephoning various people incessantly, had refused to let maids clean her quarters, and had a very poor memory. She could not get along with anyone. In the hospital she laughed at her own jokes, claimed her money was being stolen, was convinced she would lose a sore toe, was generally critical, and rejected everyone. She complained that the doctors were babies and that she should be telling the doctors and her children what to do. Although, with some difficulty, she became oriented in the hospital surroundings, she showed a considerable impairment of memory.

Her past history revealed that her father and mother had died when she was a little girl, that she had thought highly of the grandmother with whom she had lived, and that she had continually threatened and dominated her younger brother and aunt while growing up. When her future husband proposed, she said "you be at the church and I might be there." She drove her husband to success. Although she was not involved in civic duties or hard work herself, she drove others in their work and was regarded as a woman of high intellectual capacity. Her husband died when she was sixty years of age. Soon afterward she became disagreeable and stayed in bed for long periods. She could not settle upon her living arrangements. Coincident with the onset of serious lack of memory, she showed the development of more serious symptoms with accusations and delusions that others were stealing from her. When her children forced her to accept reasonable care, she became totally unmanageable.

After 2 months in the hospital she was given 800 mg. of meprobamate 3 times a day. Within 2 or 3 days her general humor changed. She still wanted to leave the hospital, but joked about it. She became manageable and ate well,

although she continued, in a lesser degree, to complain about the food. The nurses became quite fond of her because of her sense of humor. They were able to persuade her to change her clothing regularly, although she continued to refuse to clean her room. She walked a great deal and formed a close companionship with another elderly patient. Her children began to take her seriously when she insisted that they make some plan for her to leave the hospital and live in her summer home. Although she never ceased berating them when they visited her, and forced them to a completion of the plans, she remained in generally good humor and was able to convince her doctor that she should be discharged. She left the hospital in June 1956, and has remained in satisfactory condition.

Case III: poor result. A retired 69-year-old reserve naval officer and wealthy man of leisure was admitted to the McLean Hospital June 27, 1955, because of marked loss of memory and disorientation of a year's duration that had gradually developed during several years. At the hospital he was found to be disoriented, confused, to have no memory of recent events, to have a very short memory span, and to wander day and night. He was pleasant, professed to be very comfortable, and would co-operate momentarily. The main problems of management were his sleeplessness and incessant wandering.

His past history revealed the fact that his chief interest was in books, that he was loyal to the Navy, that he was very active in nonremunerative civic affairs, and that he had written a book on the architecture of small houses. Although his increasing loss of memory had been noted for several years, he tried, after recovering from a myocardial infarction, to become interested again in his books, but became agitated, threw his books on the floor, and soon required hospitalization.

Meprobamate, 400 mg., 4 times a day, was started in December 1955, and resulted in a few days of less wandering at night, but there was no other change. The tendency to wander gradually revived. In January the dosage was increased to 800 mg. 4 times a day. Again he wandered less at night for a short time, but then resumed his former pattern.

Cases I and II seemed to illustrate that deeply ingrained activities important to the patient's feeling of security and well-being could be resumed if conditions were made favorable. Hair combing, dressing, going to the toilet, and other activities connected with getting up and going to bed all appeared to be necessary for the sense of integrity of the patient described in Case I. All of these activities corresponded to periods of development when self-disciplined independent activity was initiated. Relinquishment of control over the activity by the nurse and its resumption by the patient resulted in marked benefit. The special characteristic of thriving upon driving other people to action (Case II) was not allowed to operate within the conditions of that patient's psychosis. The reversal of the trend, so that it again became plausible for her physician and her children to listen to her, seemed to be the means which again enabled her to feel better. Case III showed an unsuccessful trial of meprobamate in a patient who was not able to resume any activity upon which formerly he had been highly dependent for his well-being; he could not resume

his interest in books, he could not participate in complex community affairs, and he could not return to naval activity. No similarly motivated gratification at a lower level of development could be found to lessen his restlessness.

Each of the patients described showed gradually increasing dementia, but without marked disorganization of personality or the development of the appearance of sudden extreme dementia until the same point of intolerable frustration was reached. In Case I, increasing incontinence culminated in a failing attempt to solve a child's puzzle, followed by depression and then disorientation. In Case II, increasing memory loss, a long period of uncertainty, and paranoid tendencies culminated in the assumption of the management of the patient by the patient's children, with subsequent total unmanageability. In Case III, gradually increasing loss of memory and recovery from myocardial infarction resulted in a final surrender in the form of the patient's throwing his beloved books on the floor. Cases I and II were of such a nature that the reduction of tension by the administration of a drug allowed a partial return of the needed activity, while Case III showed no improvement with a reduction of tension.

In nine other cases it was possible to discern some of the mechanisms leading to the management problems, as well as mechanisms of the improvement or lack of improvement after administration of the drug.

It was thought earlier in the study that meprobamate was most effective for cases of mild dementia, in which a reduction of tension could bring about restoration of activities, and that it was least effective in cases of severe dementia, in which no restoration of activities could occur. Although this hypothesis probably was correct to a certain degree, some exceptions were encountered. Some of the very demented patients were capable of improvement, but some of the less demented were unable to improve if no openings for the return of satisfying activity could be found.

Two patients had been given reserpine prior to meprobamate. Both showed a general reduction of activity in response to reserpine, with a consequent increase in manageability. Shouting, resistiveness, and aggressive behavior lessened. In each case, meprobamate produced less quieting than did reserpine, even though it was given to the point of inducing sound sleep at night and considerable napping in the day. Observations made upon a number of other patients given reserpine alone confirmed the impression of the difference between the actions of reserpine and meprobamate.

Two patients were given chlorpromazine prior to the use of meprobamate. In one, an aggressive, noisy, very demented patient, there was a general quieting on chlorpromazine that could not be achieved with meprobamate. The improvement with chlorpromazine was obtained at the expense of a general decrease of alertness and integrated activity. In the other patient, administration of meprobamate was followed by a reversal of behavior from following, nagging, and demanding to sitting, watching, and laughing at the troubles of others, whereas this change was not achieved on moderate doses of chlorpromazine.

Meprobamate, as it affected senile patients, appeared to elicit responses that

can be described in two general categories. One was the hypnotic effect: improved sleep at night and an increased tendency to nap during the day. The other was the general quieting of some underlying tension, in some cases making possible changes in the quality of emotion and behavior. There was a limitation upon the dosage, because the tendency to sleep became very marked in some patients before a significant lessening of the undesirable behavior took place. In contrast, chlorpromazine and reserpine could be increased in dosage in most cases to a point where a general quieting of behavior took place, even though the activity of the person was generally dulled. In such cases extensive sleepiness did not occur. Meprobamate, like chlorpromazine and reserpine, did not appear to produce a general clouding of the remaining intellectual capacities of senile patients, as barbiturate medications may do if used to a point of effectiveness.

Summary

Meprobamate was found to be a sedative of some usefulness in the treatment of a series of twenty patients with senile psychosis. The benefits included: decrease of angry outbursts, decrease of resistance to care, increase of participation of the patient in his own care, improvement of sleep, decrease of wandering, decrease of noisiness, increase of congeniality, and decrease of the tendency to fight needed restraint.

The method of study concentrated upon an extensive questioning of the nurses regarding patients given meprobamate and others not given this drug. A number of special attitudes toward senile patients, including some misconceptions, were found to exist among the nurses and, in some areas, to impair their empathy. Complicating a study such as this were the following factors: the intimate involvement of these special attitudes of the nurses in increasing the problems of caring for the patients; the possibility that these special attitudes altered during the treatment of such patients; the possibility that these attitudes modified abstract observations; and the possibility of reaction to expectations for improvement from administration of the drug.

Most striking was the manner in which meprobamate appeared to help with certain problems of angry resistance to nursing procedures. These procedures were concerned with such activities as arising, dressing, going to toilet, and going to bed at night. When there was benefit in the field of such activities it appeared to occur by means of some initial improvement from the drug, followed by relinquishment of control over the activities by the nurse and resumption of control by the patient. It seemed that the activities in question were of lifelong and special importance to the patient in fulfilling his need to feel capable and secure. The patient's capabilities to perform these activities were strikingly intact, even though a devastation of other activities may have reduced him to an otherwise nearly vegetative existence.

Discussion of the Paper

QUESTION: There is no doubt that meprobamate causes some improvement in demented senile patients. One of the disturbing symptoms in senile pa-

tients is their incontinence. I wonder whether Bower has any information as to whether meprobamate may bring about the relaxation of the bladder that would allow greater collection of urine and would markedly improve the incontinence of elderly patients, who mostly have an organic brain syndrome with atrophy of the brain.

W. H. Bower: In those who did show improvement, there was often improvement also in regard to incontinence. I do not know whether this occurred because of relaxation of the bladder.

THE ROLE OF MEPROBAMATE IN POSTOPERATIVE SURGICAL CARE*

By Timothy A. Lamphier
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A major and frequent obstacle in the path of successful recuperation following surgery is the depression and anxiety often experienced by the patient during the convalescent period. A medicament that would help to eliminate this serious condition would be of valuable aid to the medical profession. Meprobamate (Miltown) is such a drug. It has a marked tranquilizing effect on the worried or anxious patient. It can be used in conjunction with opiates and barbiturates, making possible a definite reduction in dose when they are required, and, frequently, it can supplant them completely.

Ludwig and Berger first reported this propanediol derivative "meprobamate" in 1950,[1] and Berger described its pharmacology in 1954.[2] The chemical formula for meprobamate is 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate.

In the past few years a number of newly developed and clinically utilized drugs have proved satisfactory in avoiding postoperative anxiety, tension, and depression, but they have presented certain drawbacks in that serious complications and side reactions have often accompanied their use. Meprobamate is unique in that, up to the present time, few serious untoward reactions have been reported. Except for rare sensitivity reactions (none of which were encountered in this series), these few reactions have been of a minor nature. No case of blood dyscrasia, bone-marrow depression, or liver or kidney damage has been reported.

Early ambulation following major surgery is of vital importance in the avoidance of such complications as phlebitis, ileus, and hypostatic pneumonia. Early ambulation, indeed, today plays a vital role in routine medical care. To offer those patients who have undergone major surgery a drug that will in no way interfere with the usual postoperative program, but one that, at the same time, will alleviate the great anxiety and tension often associated with this period is not only of tremendous import to the usual postoperative regimen, but is also a great aid in the rapid and complete return to normality. Tranquilizing drugs assure relaxation. Hypnotics, such as those in the barbiturate group, are effective only in a sense. The sluggish reactions that invariably accompany this group of drugs interfere with the active program required in our modern surgical postoperative regime.

In the study upon which this paper is based it was observed, just as Borrus had reported,[3] that the tranquilizing effect achieved during a day of meprobamate administration was carried over, so that no further sedatives were required for sleep. Indeed, it was noted that the three most outstanding characteristics of meprobamate were: (1) its marked tranquilizing effect during the day when the patient was awake; (2) its sleep-producing qualities at night

* The meprobamate (Miltown) used for this study was supplied by Wallace Laboratories, New Brunswick, N. J.

without any "carry over" the next morning; and (3) its efficacy in prompting the reduction of muscle spasm. The ability to prescribe a medication that will alleviate muscular and mental tension without clouding consciousness is a great adjunct to our present-day postoperative routine.

About 10 per cent of the drug was excreted in unchanged form via the urine. Most of the drug was excreted as a conjugate with glucuronic acid about 24 hours after ingestion. Pharmacological study indicated that meprobamate had a selective blocking action in interneurons. It has been shown by Berger[2] and Hendley *et al.*[4] that, from the standpoint of muscle relaxation, meprobamate is similar to mephenesin (Tolserol), but that it has greater potency and longer duration of action. It is believed that the rapid oxidation of its primary hydroxyl group accounts for the failure of mephenesin. "In its effect on the higher centers, Miltown differs from Tolserol in producing marked synchronization of brain wave patterns. This effect is most pronounced in sub-cortical structures and particularly in the thalamus, which . . . is involved in controlling the expression of emotion and the state of awareness. Meprobamate produces its effects by blocking abnormal stimuli in the long interneural circuits, especially those between the cortex, thalamus and hypothalamus."[2]

Ordinary sedatives and hypnotics produce characteristic sleep patterns in the human electroencephalogram. Meprobamate, however, does not produce such changes. Sleep, a factor vital in convalescence, follows naturally with the reduction of insomnia-producing tension and, when meprobamate is used, the patient is remarkably free of the postbarbiturate morning hangover. "Monkeys, fed Miltown, lose their fear, hostility and aggressive behavior. They become tame and friendly."[2] In consequence the patient is much more amenable to postoperative therapy and procedures, and he co-operates readily with the doctor. In its use as a muscle relaxant, meprobamate blocks interneurons in the spinal cord, interrupting the spasm response to pain. This encourages early activity and ambulation, and it also reduces the necessity for analgesics, with their inherent drawbacks. It has also been shown experimentally in previous studies that undesirable autonomic side effects are not produced by this drug, nor does meprobamate affect peripheral nerves or myoneural junctions. Furthermore, it has been demonstrated that this compound is a drug of markedly low toxicity. Pathological changes in the liver, on blood-forming elements, or in the kidneys have not been observed. No changes in blood counts for toxicity have been noted in this study, which substantiates similar reports in previous studies.

One of the most important questions to be answered regarding any drug is whether it tends to be habit forming. In the case of meprobamate it has been shown, not only in previous evaluations, but also certainly in this study, that withdrawal symptoms are nonexistent. Furthermore, patients who have benefited greatly from the use of this drug have not asked for increased doses to maintain the original sedative effect, nor has it been necessary to wean our patients gradually, as is often the case with opiates and barbiturates.

In this study meprobamate was supplied in 400-mg. tablets and was administered orally. Three tablets were ordered daily, one before or after each

meal, with an occasional tablet at bedtime in those instances where patients had difficulty in sleeping. Unless specifically required for pre-existing anxiety neuroses, the drug was discontinued at or prior to the time of the patient's discharge from the hospital. There was no so-called "hangover" or feeling of lethargy on the morning following active therapy. Tolerance to the drug did not develop.

Of the 184 patients studied, only 4 showed any adverse reactions. Two patients experienced nausea following gastrectomy, and a third patient complained of gastric upset. The fourth reported that the drug caused a severe headache. It has been reported previously that one of the most frequently occurring side effects is drowsiness. Of course this state, provided it is not too greatly exaggerated, is important in the usual postoperative course of the patient. In this series it was encountered infrequently and was very mild in degree. Contrary to what has previously been reported in this group of patients, there were no side effects of itchy urticaria or erythematous rash. Also, there were no cases of bronchial spasm or angioneurotic edema.

In general it was found that meprobamate was a safe central-nervous-system depressant. In all of the patients studied in this group complete blood-cell counts and urinalyses were carried out on a daily scale and, in those instances in which the patient continued on the drug following discharge from the hospital, were continued on a biweekly basis. The laboratory analyses revealed absolutely no toxic effects. It was interesting to have patients state that, although in some instances the drug was ordered primarily to relieve anxiety, they derived the greatest benefit from its anti-insomnia effects.

We are all familiar with the so-called carry-over effect of the barbiturates, the bromides, paraldehyde, and other sedatives, as well as the possibility of habit formation. Furthermore, we know that tolerance to these sedatives is apt to develop. As Berger has postulated,[2] it is possibly the absence of the ring structure in the meprobamate molecule that explains the absence of so-called addictive and habit-forming properties. Also, Berger has stated that the few untoward side effects probably are related to the absence of highly reactive unsaturated leakages.

It must be remembered that, in those cases in which the drug was used to relieve spasm, only the so-called skeletal or voluntary muscles were affected. Even when meprobamate was taken in large doses, its toxicity was extremely low.

One may conclude that the benefits of the drug in the average postoperative patient are due in large measure to its ability to alleviate the unusual anxiety-tension state created by: (1) recent major surgical procedure and (2) the need to remain bedridden or at least hospitalized for a prolonged period of time. The tension that often prevents sleep is alleviated or done away with by the action of meprobamate on the thalamus.

Several investigators have noted that some patients, although complaining of drowsiness when first given meprobamate, responded well if the medication was reduced in the beginning and was later increased until the ultimate desired effect was obtained.

TABLE 1

TABULATION OF POSTOPERATIVE THERAPEUTIC RESULTS WITH MEPROBAMATE

Surgical procedures	No. of patients	Satisfactory therapeutic result	Unsatisfactory or no therapeutic result	Reaction
Panhysterectomies	60	60	0	0
Open reduction of fractures	32	30	1	1
Gastrectomies	35	31	2	2
Miles' resections	15	15	0	0
Thyroidectomies for toxic goiters	30	28	1	1
Laparotomies—metastatic cancer	12	12	0	0
Total no. of patients	184	176	4	4

Thus far, the majority of studies have had to do strictly with the tranquilizing effects of the drug.

Clinical Study

The clinical evaluation was based on the use of meprobamate in postoperative care following major abdominal surgery for the majority of the 184 cases studied (TABLE 1). Most of the patients in this series would normally have required some type of barbiturate either to achieve sleep or to alleviate extreme nervousness. I treated most of the patients in this group myself. To assess to a finer degree the efficacy of the drug, I asked several of my surgical colleagues to appraise its effectiveness so that the end result would not be the opinion of only one investigator.

At the outset of this study we made an attempt to compare the advantages of intramuscular meprobamate with oral tablet administration. No real difference was noted. In those instances where patients were disturbed by nausea or vomiting, the drug was administered intramuscularly.

The average dosage consisted of one 400-mg. tablet 3 times a day, usually about mealtime. In a few instances the dosage was increased to 4 or 6 tablets daily and, rarely, it was decreased to only 2 tablets daily. The nocturnal soporific effect was sufficiently effective to obviate the need for any allied therapy, although only 10 patients complained of drowsiness during the daytime. In more than 50 hemorrhoidectomies (not included in this study) treated with meprobamate there was a pronounced reduction of sphincter spasm and, in turn, of postoperative discomfort.

Discussion

A marked co-operation of the patients in postoperative regimens, as in carrying out exercises and following diets, was observed. Several of those patients who underwent gastrectomies had been heavy drinkers of alcohol, and the emotional strain in this group was noticeably reduced. Two patients in the gastrectomy group complained of nausea, and the drug was discontinued.

An outstanding finding in those patients who had been previously addicted

to barbiturates for a "good night's sleep" was the fact that a gradual withdrawal or even an abrupt cessation of the barbiturate and its replacement by meprobamate induced sleep. Follow-up studies after discharge from the hospital demonstrated, in general, no habit-forming characteristics.

The great mental disturbances that accompany panhysterectomy, with its attendant change in hormonal balance, were lessened by the administration of meprobamate as an adjunct to hormonal therapy.

In cases of fracture, good muscular relaxation was obtained.

For terminal care in patients with carcinomatosis there was a distinct beneficial effect when meprobamate was combined with the opiate groups. This effect had previously been reported by Kessler and Barnard.[5]

Summary

In comparing the results achieved in these patients with the findings obtained in a parallel group who were given placebos, it was noted that there was a gradual restoration of equanimity and that, in general, the patients were much more co-operative. The patient-to-patient relationship was a more amiable one. Actually, the equanimity was obtained without mental depression, and a keener perception was often noted in those patients receiving meprobamate. The emotional strain in the alcoholic patients who were bordering on delirium tremens was relieved. There were no reported cases of nausea or vomiting in this group, nor were there any so-called accumulative effects. Dermatological reactions were likewise absent. As stated above, the blood and urine were always within normal limits. In the orthopedic group the drug had a relaxing effect and it definitely reduced spasm. There was no effect on the autonomic nervous system, on the heart, or on respiration. The dosage could be adjusted easily, either upward or downward, without giving too much thought to toxicity.

Conclusion

Of the 184 patients who underwent major surgery and were treated with meprobamate to expedite and abet their postoperative course, 176 received definite therapeutic benefits without courting the danger of addiction or depression frequently seen when opiates and barbiturates were used. It may be concluded, therefore, that meprobamate is a definitely desirable adjunct to the postoperative management of the surgical patient.

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Discussion of the Paper

QUESTION. What about the placebo group mentioned in the summary?

T. A. LAMPHIER: We tried the patient on placebo for two or three days and then changed to meprobamate, having several people note the presence or absence of differences in response.

QUESTION: I notice that Lamphier has discussed at some length the postoperative treatment with meprobamate. I wonder if he has given any consideration to the preoperative preparation of patients with this drug, preparing them for what the operation might represent to them and the anxiety that this knowledge involves. Also, he seemed to indicate in the paper that, after the completion of surgery and the discharge of the patient from the hospital, treatment was immediately suspended. I wonder if he has considered also the needs of the patient postoperatively following his discharge from the hospital, the anxieties aroused by such procedures as colostomies, inlying catheters, and many other postoperative appliances with which patients have to cope and to which they must become adjusted.

T. A. LAMPHIER: We are now studying the preoperative use of meprobamate on a large number of patients. The treatment is started at least a week or ten days prior to surgery or admission to the hospital, because we feel that during this period most patients who are to undergo a major procedure will be under a fair amount of tension and apprehension.

Regarding the use of the drug postoperatively and the suspension of the treatment when the patients are discharged from the hospital, in a few instances we have found that patients did need to continue the drug at home.

For example, with the patient who undergoes a Miles' resection I make it a rule never to discuss the type of procedure preoperatively with the patient. Postoperatively, of course, there comes a day of reckoning and, usually about the fifth or sixth postoperative day, I must sit down with the patient and tell him that he no longer has a rectum, but has a permanent colostomy. There is a point where a severe depression develops and, certainly in some of the female patients on whom I have operated, I have continued using meprobamate with their return home, but always with the idea that within a period of three to four weeks I shall discontinue the drug. Once the patient gets used to the idea that he or she can live with a colostomy bag without any fear of embarrassment of being different, usually the meprobamate can be discontinued.

AN EVALUATION OF MEPROBAMATE IN THE TREATMENT OF ALCOHOLISM

By Leon A. Greenberg, David Lester, Alexander Dora, Robert Greenhouse, and Joseph Rosenfeld

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Tension states are a prominent and probably basic causal feature in the behavior called alcoholism. In treating the alcoholic, therefore, the therapist has felt the need of and has sought for an ideal sedative or relaxant drug having maximum and consistent effectiveness and presenting a minimum liability of addiction, overdosage, intoxication, or other unwanted side reactions. During the last several years a number of new drugs have appeared, each intended fully to meet these requirements; the appearance of each has presented the physician with the difficulty of selecting the drug of maximum relative value. As a basis for making a selection, he has had to rely largely on the clinical impressions of others. These conclusions have been drawn from observations often lacking in adequate control and significant numbers and involving wide differences as between the various observers and drugs and the particular aspects of symptomatology with reference to which the impression is formed. It is apparent that any judgment of the relative merits of agents intended for a given disturbance requires, for its maximum validity, the application to each drug of the same adequate test design and a uniform consideration of the symptoms of the disturbance, that is, the same yardstick. It was with this purpose that the present clinical evaluation of meprobamate in the treatment of alcoholism was conducted, in the hope that other drugs intended for such treatment eventually might be tested similarly.

The present study of meprobamate was made on 167 alcoholics. One hundred of these were hospitalized patients exhibiting the more acute and pronounced phases of psychomotor agitation, anxiety, irritability, nervousness, apprehension, and other symptoms of hangover that, in general, were the reasons for their hospitalization; 67 were ambulatory chronic outpatient alcoholics. In both of these groups half of the patients received the drug and half received the placebo, neither the patient nor the therapist knowing in any instance which was given. The outpatient subjects received 1.6 gm. of meprobamate daily (q.i.d.) for a period of 3 weeks and were seen by the therapist at weekly intervals. The hospitalized patients received an average of 2.4 gm. daily during their stay in the hospital of from 1 to 2 weeks.

While the physician's total impression of the patient's progress is the result of his observation of a variety of pertinent discrete symptoms, the weight given to any particular symptom in forming this impression may vary considerably from one observer to another, from one patient to another, and from occasion to occasion. Such impressions alone therefore are often inadequate as a basis for the quantitative comparison of two or more drugs. For the purpose of the present study we drew up a list of what the therapists felt to be the more significant symptoms and signs in the alcoholic patient. This list incorporated

Case Number: Sex: Age:

Admission Number:

Admission Date:

I. SYMPTOMS AND SIGNS	DATE:						
Psychomotor Agitation							
Anxiety							
Irritability							
Adjustment in the Hospital							
Craving							
Hallucinations*							
Insomnia							
Depression							
Demand for Medication							
Convulsion							
Anorexia							
Nausea							
Vomiting							
Diarrhea							
Constipation							
G. I. Distress							
Alcoholic State**							
II. PHYSICAL EXAMINATION							
III. LABORATORY RESULTS							
IV. MEDICATION TAKEN							
Drowsiness							
Idiosyncrasy							
Libido							
Other							
V. REMARKS							

* Hallucination: Visual = V+; Auditory = A+ or AV+; Tactile = T+ or AVT+.
** Alcoholic state: Sober = S; Hangover = H; Under the influence = U; Intoxicated = I; Comatose = C.

FIGURE 1. Clinical evaluation chart.

the general impressions in the data sheet used in every case (FIGURE 1). On admission to either the outpatient clinic or the hospital, the status of each patient with regard to each of these symptoms was recorded. A similar record was made thereafter on every examination; in the hospital patients, at the end of the experimental treatment period, the therapist's impression of the

TABLE 1

PER CENT OF IMPROVEMENT OF SYMPTOMS IN OUTPATIENTS

Symptoms	Meprobamate	Placebo	*P*
Psychomotor agitation	82	40	0.01
Anxiety	88	33	0.01
Irritability	82	32	0.01
Craving	67	38	N.S.
Insomnia	89	38	0.01
Depression	85	48	0.05
Demand for medication	50	10	0.01
Anorexia	62	41	N.S.
Total	76	34	0.01

extent of general improvement was included. Such data, uniformly describing the initially existing pertinent symptoms and remissions under treatment, are amenable to better statistical analysis and therefore afford a more exact basis for evaluating the effectiveness of the drug.

The results of the study with the outpatients were clear. These are shown in TABLE 1. Of the symptoms included in the data forms, only eight were present initially in significant number in the patients studied, namely, psychomotor agitation, anxiety, irritability, craving, insomnia, depression, demand for medication, and anorexia. In all but craving and anorexia the difference in effect between drug and placebo treatment was large and highly significant statistically. With craving and anorexia the difference was also considerable, but not statistically significant, although the trend was very apparent and the effectiveness of the drug was strongly suggested. The difference in the mean percentage of remission of all of the symptoms as between treatment with meprobamate and placebo—76 per cent as compared with 34 per cent—is considerable, and the statistical significance is high. In the outpatients, meprobamate was clearly an effective drug.

In the hospitalized patients observed in this study the disturbance was of a more acute and severe order. As seen in TABLE 2, the only recorded symptom that showed any considerable and statistically significant difference between drug and placebo treatment was insomnia: 76 per cent as compared with 22 per cent. However, the impression of general improvement, as recorded by the therapist in each case, showed a striking difference between drug and placebo treatment with a high degree of statistical significance. The impression of improvement was recorded as either excellent, good, questionable, or negative.

TABLE 2

PER CENT OF IMPROVEMENT OF SYMPTOMS IN HOSPITAL PATIENTS

Symptoms	Meprobamate	Placebo	*P*
Insomnia	76	22	0.01
General improvement	64	10	0.01

Taking excellent or good as successful treatment and questionable and negative as failure, 64 per cent of those treated with meprobamate were improved, as compared with only 10 per cent of those treated with placebo.

In the judgment of excellent or good improvement, several of the following changes were observed: there was a perceptible relaxation without drowsiness or loss of alertness. The duration of complete recovery from intoxication was shortened, and the intensity of "hangover" symptoms was greatly diminished. The need for additional medication in the early acute stages was remarkably lessened, although in many instances it was still required in smaller amounts and less frequently. The continued demands of readmitted patients were much less, and their satisfaction and general behavior were much better as compared with their previous hospitalizations when they received other drugs. The patients slept well, with no aftereffects the following morning. In general, it was unanimously agreed by all members of the professional staff of the hospital in regular and close contact with the patients that, in those treated with meprobamate, management was surprisingly easier. The patients were more amenable, the males were more respectful toward the nursing staff, and the females were less demanding of attention and sympathy. They were all less noisy among themselves and more prone to partake in group activities or discussions. The characteristic alcoholic clinic environment of tension, impulsiveness, restlessness, adolescent noisiness, and aggression was appreciably diminished.

It is noteworthy that, in the hospital patients and with reference to the individual symptoms recorded on the work sheet, with the exception of insomnia no significant difference was perceptible between the drug and placebo treatment. In view of the apparent effectiveness of meprobamate in the outpatients and in other aspects of the hospitalized patients, the only explanation that can be offered for this is the fact that the adequate treatment of half of a group of alcoholics, through identification or fear, or through the witnessing of successful results on the questionably successful patient, will increase the tolerance of the alcoholic to his inner stresses by increasing his own anticipation of benefits. In the hospital situation the patients are in close and continuous association with each other. Unlike the outpatients, they are also in frequent contact with the hospital staff who try continuously to satisfy their varying needs. All of these factors undoubtedly function so to increase the apparent improvement in certain aspects of the patients receiving placebo as to diminish below the level of statistical significance any difference between this response and the response to the drug.

Apart from occasional drowsiness, side reactions were few and of doubtful origin. These occurred in the hospitalized patients receiving maximum doses and were immediately relieved by diminishing the dosage. In a severely disturbed outpatient who consumed 22.4 gm. of meprobamate at one time there were no ill effects other than marked drowsiness and some vomiting. The observations made in the present study of meprobamate warrant the conclusion that its use in the treatment of alcoholics offers advantages. In the subacute and chronic patients its use would appear to be highly recommended; in the acute stage it is useful as an adjunct to other medication.

Discussion of the Paper

QUESTION: Were the doctors within the hospital able to tell which patients were on meprobamate and which were on placebo? Were two groups used, one receiving medication *A* and the other receiving medication *B*; or were other markings used, so that the patients could not be divided into two groups?

QUESTION: I was wondering if Greenberg and his associates have ever tried giving a placebo to inpatients, not as a control, but just giving a placebo and noting the response when the staff does not know that a placebo is being given. It has not been clear to me whether or not this was a double-blind study or whether the staff knew who received meprobamate and who received placebo.

A. DORA: It was a double-blind study. The therapist did not know, at least he was never told, which dosage was drug and which was placebo. In both the outpatient situation and in the hospital before the study was half completed, the therapists were expressing a knowledge of which was which. Nobody told them, but they were observing the patients and, although they would make comments to us in the laboratory, we revealed nothing. I can say, however, that the therapists did know that one dosage was yielding better results than the other although, in some instances, there was an apparent effectiveness of as high as 40 per cent with placebo.

J. ROSENFELD: I am the psychiatrist in charge of the inpatient facility. We have five outpatient clinics, removed from the hospital, and in these facilities the patients are treated. The outpatients come by way of the hospital. A patient rarely seeks treatment in an outpatient clinic prior to hospitalization, and he is treated in the outpatient facilities right up to the completion of treatment. As a rule, sooner or later most patients will have to undergo periods of hospitalization.

We admit frankly that the physicians knew fairly quickly which dose was having the effect and which was not. It took the nurses a little longer. It took the attendants a little longer than the nurses, but the patients did not know. We did not know officially, but we could make an assumption, and the interesting thing is that at first we went off the true path by trying to gauge symptomatology, anxiety, ability, and adjustment to others; but eventually we could tell who was getting the placebo and who was getting the drug.

The bottles containing the medication were small, numbered, and all the same size and color.

QUESTION: Has the value of the drugs been clarified in treating patients in a hostile state or in an acute condition? Did this study refer to individual patients who were long term or short term? What was the availability of alcohol on the outpatient level and the availability of alcohol in the hospital?

J. ROSENFELD: These are all patients who have been diagnosed as alcoholics, so there is no short-term illness, but only long-term illness. The hospital patient is in an acute state that includes intoxication or hangover or, during the hospital period, he goes from intoxication to hangover. He remains in the hospital a short time and then is released and followed up by the outpatient clinic. Some of the patients have been in the hospital three, five, or six times.

For many it is the first admission. In most cases, upon leaving the hospital they go to the outpatient clinic. If they come from a psychiatrist or a general practitioner who is treating them for alcoholism, we merely return them to him unless he is willing to let them come to the outpatient department.

QUESTION: I should like to ask whether any therapy other than meprobamate, such as psychotherapy, would also be used, and whether any cures have been effected after a prolonged period of therapy.

J. ROSENFELD: We have a setup in the Connecticut Commission that, in all respects, is carried on exactly as though we were not working any experiment at all. Only the drugs are changed. We give no barbiturates and no paraldehyde, but we have regular group-therapy situations and interviews with psychiatrists. The medical men see their patients daily on request or on recommendation by the nurse. In group meetings the patients meet every day, seeing a social worker in one session and seeing me in another session. Private interviews with me are held the regular way. Occupational therapy is also done.

H. C. SOLOMON (*Harvard Medical School and the Boston Psychopathic Hospital, Boston, Mass.*): Can the speaker tell us how his results compare with the results obtained with other drugs in the control of postalcoholic states? It would interest me a great deal also to know what happens when no drugs are used on these patients, because we have used no drugs whatsoever in our institution for years, unless it was done surreptitiously, without my knowledge.

J. ROSENFELD: What you are asking, of course, is why are we lagging behind? We are gradually trying to achieve what you have achieved, that is, complete avoidance of the use of drugs, but we do not have a Solomon on the Commission. Beginning with the period of reserpine, we started to cut down from tons of barbiturates to thousands of pounds, and when we got chlorpromazine we reduced to hundreds of pounds. Gradually we have reached the stage where we use barbiturates only for conditions other than alcoholism. We stopped buying paraldehyde. We use chlorpromazine as p.r.n. order. Now, if a drug does not work on a d.t. or a hallucinotic patient, we can still take him. If he develops a Korsakoff's psychosis we do not ship him out until he is sufficiently ambulatory.

In all dehydrated cases, in all patients with severe loss of weight, or in patients showing the general symptomatology, we give an intravenous infusion of glucose-saline, sometimes with insulin, sometimes without. We hope eventually to achieve the stage of no drugs; when we get very courageous we shall try to hold a fairly intoxicated patient with acute hangover without using drugs other than vitamin B.

QUESTION: I wonder if your work would be of any help in suggesting the areas of the brain in which the drug may exert its principal effects. What I am thinking about is the possibility of a different effect in severe chronic alcoholics as compared with those who are outpatients.

J. ROSENFELD: I can only quote the literature. As a result of the difference in the two study groups, the outpatient and the inpatient, I do not think we have in any way discussed the question of just where the drug works. I shall continue to go along with the synapse.

THE TREATMENT OF CHRONIC HEADACHE WITH MEPROBAMATE

By Arnold P. Friedman

Division of Neuropsychiatry, Headache Unit, Montefiore Hospital, New York, N. Y.; Presbyterian Hospital Neurological Institute, New York, N. Y.; and Neurological Institute, Columbia University College of Physicians and Surgeons, New York, N. Y.

The incomplete and often unsatisfactory results of interim therapy in the treatment of chronic headache have led to the yearly introduction of a number of new drugs. The purpose of this paper is to report my results with one of these new chemical agents, meprobamate, in the treatment of chronic headache.

I should like to begin by making some general remarks concerning the evaluation of drugs in patients with chronic headaches (FIGURE 1). From a standpoint of pharmacology we must consider the action of the drug, the mode of administration, the dosage, the timing, and the tolerance of the patient. In addition, because the administration of a drug is always associated with an emotional effect, factors other than the pharmacological action of a drug are of great importance. The significance of emotional factors on the action of drugs is well known, but it has not always been considered in evaluating the effects of a specific agent. We have pointed out how greatly the interpersonal relationships between the physician and the patient can modify its effects, even when the drug is given in the same dosage at different times to a patient with headaches. Bleuler[1] summarized this quite well when he stated: "The equation between doctor and patient must always be considered even in actions that seem to belong to strict natural science like giving a drug which has been experimentally proven."

Another factor to be considered is the types of personality often found in patients with chronic headache. A patient with a meticulous, rigid, or perfectionistic personality, or with strong aggressive drives, may have a psychological resistance with a negative transference causing him to react unfavorably to the therapy. Furthermore, the symbolic significance of the therapy is an important contributory factor in the result of treatment. Does the patient regard the acceptance of medication as a sign of weakness, or does it signify the receipt of omnipotent mystical power, or of love and affection? In other words, the effect of a drug for treatment of chronic headache depends not only upon the medication itself, but also upon the personalities of the patient and his doctor. Therefore it is obvious that the effectiveness of a drug is not only difficult to evaluate from patient to patient, but even in the same individual during different periods of observation.

The pharmacology of meprobamate has been discussed in previous papers and no review of this subject will be undertaken in this report.

Material and Methods

This study, extending over a period of 20 months, included patients in the Montefiore Hospital Headache Unit and in private practice. During the course

FACTORS INFLUENCING RESULTS OF TREATMENT

PHARMACOLOGICAL	PSYCHOLOGICAL
A. SELECTION OF PROPER MEDICATION	A. PERSONALITY
B. MODE OF ADMINISTRATION	B. PATIENT-PHYSICIAN RELATIONSHIP
C. DOSAGE	C. SYMBOLISM OF MEDICATION TO PATIENT
D. TIMING	D. ENVIRONMENTAL FACTORS
E. TOLERATION	

FIGURE 1

of the study a total of 210 patients were studied by 5 physicians. The patients were a heterogeneous group that had in common the complaint of chronic, recurring headaches that, in most cases, had been present for more than 2 years. The great majority of the patients had previously received numerous forms of medical treatment without satisfactory or lasting results. All of the patients in the study were started on meprobamate or placebo therapy at a time when they were complaining of frequent headaches. Since the patients were ambulatory and not hospitalized, their environmental influences varied greatly. One hundred and thirty-two were female. Their ages ranged from 21 to 65 years, the majority being between the fourth and fifth decade. The patients were divided into either migraine- or tension-headache groups. Whenever possible, all placebo-fast patients were eliminated from the study. About half of the study was conducted in a double-blind fashion; the physician in this group did not know which pills he was giving any patient at any time. Each initial period of drug trial lasted approximately 4 weeks. The clinical picture and physiological mechanisms of these types of headaches have been discussed in previous communications and will not be reviewed in this paper.

It should be emphasized that these drugs were used as a preventative or prophylactic form of therapy and were not given to relieve the symptoms in an attack of headache.

The dosage plan for meprobamate was as follows: The initial dose was 400 mg. 3 times a day orally. If the patient, after approximately 2 weeks at this dose level, was not showing sufficient improvement, the dose was raised in an attempt to secure a satisfactory clinical response. The highest daily dose used was 4000 mg. The majority of patients required no more than 400 mg. 4 times a day (1600 mg.). It is of interest to note that patients given the very high doses did not usually respond favorably to the drug. Placebos were given throughout the study in the same manner as the drug. All placebos were made to match the drug and were identical in size, shape, and color.

FIGURE 2. Treatment of headache with meprobamate.

Results

The patients were rated as improved or not improved. The term improvement was used to denote complete freedom from headaches or a significant decrease in their frequency. The same criteria were used in determining the placebo response. The patients were studied for a period of 3 to 14 months. Of the 210 patients receiving meprobamate, 150 had tension and 60 had migraine headache. Improvement was noted in 55 per cent of the migraine patients and in 67 per cent of the tension-headache patients (FIGURE 2). The results must be compared with our present placebo response of approximately 58 per cent improvement in migraine and 46 per cent in tension headache, and with previous reports of favorable placebo response in 50 per cent in migraine and 58 per cent in tension headache.

In a previous study, 169 patients with migraine and tension headache were given Thorazine and 380 patients were given reserpine (FIGURES 3 and 4). Of those patients receiving reserpine, improvement was noted in 45 per cent of the migraine- and 49 per cent of the tension-headache patients. In patients receiving Thorazine, effective results were achieved in 47 per cent of the migraine patients and in 52 per cent of the tension patients.

A comparison of therapeutic results with meprobamate and reserpine in the same patients who had tension headaches was carried throughout the study. Of the 58 patients receiving both drugs during alternate periods, 53 per cent responded similarly to both drugs, 9 per cent responded more favorably to reserpine, and 38 per cent responded more favorably to meprobamate. In comparing 40 tension-headache patients who received both meprobamate and Thorazine during alternate periods, 60 per cent responded similarly to both drugs, 12 per cent responded more favorably to Thorazine, and 28 per cent responded more favorably to meprobamate.

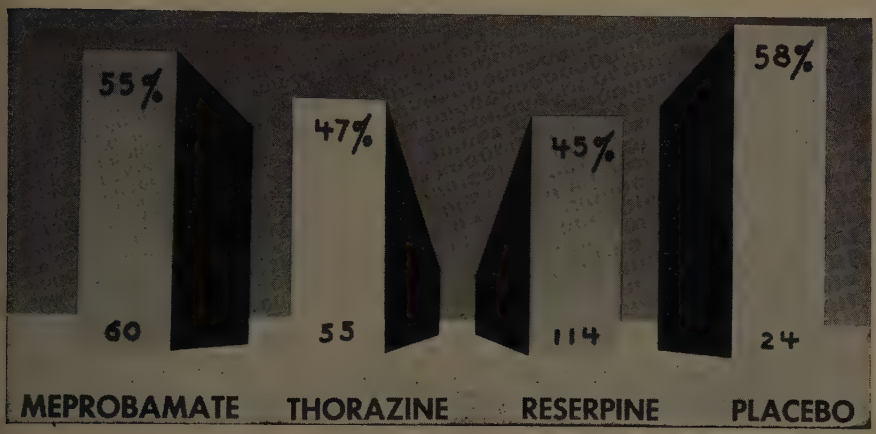

FIGURE 3. Treatment of migraine headache.

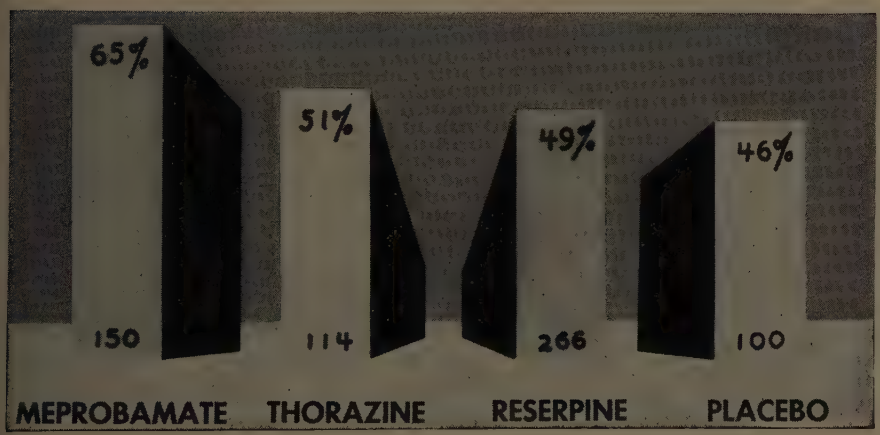

FIGURE 4. Treatment of tension headache.

Side effects in the patients treated with meprobamate were noted in only a small number of patients. The side reactions observed can be summarized as follows: drowsiness, sense of fatigue, nausea, and dizziness. In patients taking large amounts of meprobamate, amphetamine derivatives were useful in counteracting the drowsiness and the sense of fatigue when these reactions became very severe. Nausea was frequently controlled by having the patients take their medication at mealtime or with sufficient liquids. In many instances, reduction of dosage caused these symptoms to disappear. There were no instances of agranulocytosis, skin eruption, or jaundice. No evidence of addiction was noted.

Discussion

It has become clear that evaluation of the effectiveness of drugs in patients with chronic headache is a difficult task that requires controlled studies in a large number of patients over a long period of time. Furthermore, objective differences between two drugs that are both reasonably effective are difficult to determine; it cannot be predicated with certainty which patient will respond best to which form of drug therapy.

Our experience and that of other investigators has indicated that most headaches are caused by an altered state of certain vascular and muscular tissues within and outside the cranium that are related to the individual's reaction to life's stresses. It is unlikely that meprobamate could change the basic physio-psychological factors that cause the migraine-producing cranial vascular changes. The drug seems to be more effective in reducing the emotional tension and stress associated with tension headaches. Despite the fact that the response to the drug was more favorable than to a placebo, previous experience with placebos indicates that the difference may not be so significant. In some patients the spectacular results obtained with the use of these drugs suggested that the effect may be specific. It would appear that the drug effectively reduced emotional tension and reaction to stress. Furthermore, we must emphasize the point that we cannot consider the placebo effect to be the sole result of an inert substance given to the patient in the form of a pill; in any therapy there occur many nonspecific or placebo effects.

Our studies indicate that meprobamate is a more effective drug in the treatment of chronic tension headache than other tranquilizers studied. The present evidence of some success is encouraging and warrants further research with this drug.

Another advantage of meprobamate over other tranquilizers studied is that it has fewer side effects. This enables the physician to secure better therapeutic results, both physiological and psychological, with his patients. It must be emphasized, however, that drugs cannot replace insight and understanding into one's emotional problems; in this respect, their essential value lies in their capacity for reducing emotional tension, thus enabling the patient to handle his stressful situations more effectively.

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Discussion of the Paper

Question: I wonder if Friedman noticed any ataxia or muscle weakness in the dosage range he studied, particularly in the higher dose level.

A. P. Friedman: We did not have many patients on 4000 mg. a day, which was the maximum dose. I recall no evidence of ataxia with this maximum dose. Patients did complain of a great deal of fatigue and some weakness, and they were not very animated. In those cases where we used higher doses, amphetamine was used in conjunction with the drug.

QUESTION: What is the percentage of purely psychological treatment of those headache patients who did not receive simultaneous administration of the physical placebo? In other words, does the patient have a purely psychological placebo and meaningful psychotherapy in the group? I think the study is very well controlled. I believe that if the psychological factors are mentioned, there should also be introduced one group, a psychological group, for example, and another group representing a psychological placebo technique in which nonpsychological matters are discussed in a friendly manner.

A. P. FRIEDMAN: When we speak of supporting psychotherapy in relationship to a drug, where do we start and where do we stop? In other words, what is supportive psychotherapy? When we administer a drug, what is the interpersonal relationship? How many dynamic factors are being placed in action when the patient sees the physician? In all cases at the Headache Unit we have attempted to have our physicians spend a reasonable amount of time with each patient. Thus, each one of the patients seen does have some supportive therapy and, possibly, some directive type of therapy—that is, some environmental manipulation and ventilation.

Some time ago we ran a series of studies on chronic headache, in which we tried psychotherapy alone versus psychotherapy and supportive drug therapy. It seemed that psychotherapy (if given at a deeper level, with much more frequency than the routine sort of therapy) and drug treatment were effective but, surprisingly, the statistics were not greatly different. As I remember, we had 70 and 80 per cent good results, in other words a 10 per cent variation, but the number of times the patient saw the physician and the length of the interviews seemed to be the most significant point in that series.

QUESTION: I should like to know whether there is any great difference in effect on headache between mild analgesics and the tranquilizers.

A. P. FRIEDMAN: We do not use tranquilizers symptomatically. We use them in preventive, interval therapy. The analgesics are used for an attack of headache. Hence, there is little means of comparing the results achieved with the two. In general, I should say that they are used in different areas of therapy.

CLINICAL EVALUATION OF MEPROBAMATE IN DISTURBED AND PREPSYCHOTIC CHILDREN

By Harry R. Litchfield

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In conducting a general clinic for the treatment of a wide variety of disorders and diseases of childhood, one of the foremost pediatric challenges is presented by the markedly restless, irritable, aggressive, or tense child who has become a problem both to himself and to his family.

In previous years these children were handled with such mild sedatives as barbiturates and paregoric or, when possible, with superficial psychotherapy. The more recalcitrant cases were referred to the child psychiatrist. In the last several years, however, we have seen the development of an entirely new group of drugs, generally designated as the tranquilizers. A considerable amount of work has been done and reported in the literature on the use of chlorpromazine, reserpine, and the antihistaminics with these disturbed children[1] although, for the most part these studies have been conducted with the more severely disturbed children confined to frankly psychiatric hospitals or clinics.

In contrast, the study reported here was conducted with ambulatory patients in an outpatient clinic, none of whom was considered sufficiently ill for specialized psychiatric treatment, but all of whom were of the type the average pediatrician sees in his general practice. An analysis of the recent literature on tranquilizers in general seemed to indicate that chlorpromazine and reserpine were of primary value in the severely psychotic patient, whereas meprobamate, while useful in the psychoses, appeared to be the drug of choice in the ambulatory outpatient where symptoms of psychopathology consisted primarily of anxiety and tension. According to the chemical structures of these tranquilizers (FIGURE 1), meprobamate is the simplest and the least toxic.

In this series of 28 pediatric cases, all were given systematic follow-up over a period of 6 months. The main group studied consisted of 15 children between the ages of 4 and 8, with 5 other cases between 2 months and 4 years, and 8 cases between 8 and 16 years. In the 8- to 16-year group there were 3 epileptics of the *petit mal* type.

In the younger group the symptomatology consisted of marked restlessness, irritability, and sleeplessness. Illustrative of the investigation of this age group is the case of E. G., a 4½-month-old male infant born on November 1, 1955, with a body weight of 7 lb. 6 oz. History revealed that, from birth, the child had cried continuously, without tears, assumed unusual postures, and slept very little. He had been hospitalized twice; provisional diagnosis on the first admission was the Riley-Day syndrome. X-ray examinations of the chest, extremities, skull, abdomen, and spine were all within normal limits. A gastrointestinal series showed a normal stomach and intestines. Laboratory work-up, including a spinal tap, was negative. Prior to admission, phenobarbital and other sedation had been administered without any effect.

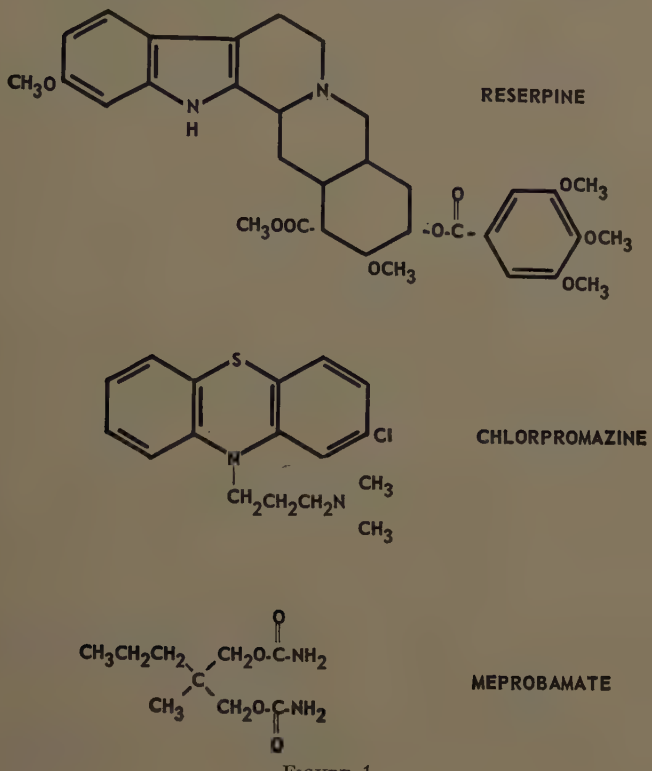

FIGURE 1

On March 31, 1956, the infant was given 200 mg. of meprobamate twice daily. Within 3 days his condition improved greatly. He stopped crying and slept at longer intervals between feedings. After 1 month the dose was reduced to 200 mg. a day in divided doses (the medication was crushed into powder and added to cereal feedings) and was continued for 4 months without any side reactions. The child became relaxed, took feedings, and gained weight. The family moved to Baltimore, and the last report, October 9, 1956, was "doing very well."

In the 4- to 8-year-old group the children seemed to be unresponsive to home discipline and were overactive and destructive. In several instances both parents were employed. A typical case in this group is that of J. G., an 8-year-old male child born June 21, 1948, with a body weight of 7½ lb. I first saw this child on March 31, 1956. The mother stated that the boy had been a problem since he was 1 year of age, had lately been fatigued, restless, and irritable, and showed nervous tendencies. X-ray examination of the skull was negative. Blood and urine examinations were negative. Blood pressure was normal. A school psychologist had reported signs of early depressive states, with changes manifesting excitability. Because of this, the child had been refused admission to public school, but recently had been admitted to a special

class for nervous children. After a complete examination and a discussion of the case with the mother, the child was put on 200 mg. of meprobamate, three times a day. On his next visit, April 7, 1956, the mother stated that he showed marked improvement in behavior, was not irritable, and seemed to be less excitable. After 3 weeks on 600 mg. a day, he was placed on a maintenance dosage of 200 mg. of meprobamate before retiring. Since then, blood and urine examinations have all been normal. Recent examination showed great improvement in the child's behavior, less excitability and restlessness, and a new interest in his surroundings.

In the older group the children seemed to be unresponsive to home discipline. Many were very aggressive in type and appeared to be laboring under tension. Some of them had underlying emotional upsets associated with medical ailments such as asthma. Some also manifested symptoms of nail biting, masturbation, uncontrollable temper, and poor response to home discipline. The need for positive treatment was evident in these emotionally disturbed and prepsychotic adolescents.

The medication seemed to stabilize their emotional upsets. They became more relaxed and, in some instances, more cheerful and amiable, and much more amenable to treatment.

The children who had definite *petit mal* attacks were very irritable, even though they were controlled by anticonvulsive drugs. The epileptics benefited in that they became more co-operative and less irritable. There is strong evidence that meprobamate alone, with its minimal toxicity, is the drug of choice in *petit mal*.[2]

From these findings it appears that meprobamate is a very effective agent in treating the symptoms of irritability, sleeplessness, and restlessness, both in the infant and the older child. The older child apparently loses his apprehension and relaxes at least sufficiently to show good evidence of ability to behave within a normal pattern. These patients also appear to benefit in their physical aspect; they seem to eat better, sleep better, and become more co-operative.

In a placebo control series of 16 cases, 3 cases in the 2-months to 4-year-old group, evincing similar symptoms, gained no relief. Eight cases in the 4- to 8-year group, under similar observation, showed no improvement in their symptoms. Five cases in the 8- to 16-year group, under placebo therapy (1 case of epilepsy included), also failed to respond.

Six cases from the treated group are still under follow-up treatment. So far they have shown no side effects. In all there has been noted a gain in weight and in general well-being. In 2 cases it was necessary to discontinue the treatment because, after 10 days in one and 3 weeks in the other, they refused to take any medication.

The medication was given according to the severity of the symptoms. The dosage was either increased or decreased, depending on the results. In the 2-months to 4-year-old group it was found that as little as 50 mg. would control the restlessness, and that 100 mg. in divided doses would be more than sufficient. The 4- to 8-year-old group responded well to 200 mg. twice daily. The older group did well on 400 mg. daily, in divided doses. This low dosage

was in marked contrast to the much higher dosage of approximately 400 mg. twice to four times a day for children from 6 months to 8 years of age, and as much as 800 mg. four times daily in children over 8 years of age taken from groups of more severely disturbed and psychotic children treated in some of the larger psychiatric institutions.[3]

Only in rare instances did we find any drowsiness, and this occurred only upon awakening, when the drug had been taken at bedtime. In the older group (8 to 16 years of age), and only when dosages of more than 800 mg. daily were taken, was there any evidence of a side effect such as drowsiness. No instance of toxic allergic reaction, blood dyscrasia, or liver or renal damage was encountered in this series.

Meprobamate has a synchronizing selective action on the thalamus without simultaneously affecting or depressing other subcortical structures or the cerebral cortex.[4-6] Likewise it has a marked blocking action on interneurons at the spinal-cord level,[4, 7] producing muscle relaxation that further tends to tranquilize the tense and anxious child. This selective activity, with sparing of the higher cortical levels, produces a tranquilizing effect without dulling of consciousness, disturbance of the mental faculties, or hypnosis.

In no instance did we find that this medication, in young or older children, retarded their mental abilities.

Conclusions

Meprobamate is the drug of choice in the treatment of a wide variety of children of all ages manifesting prominent symptoms of anxiety and tension, with or without organic disease, who are seen and treated primarily by the practicing pediatrician on an ambulatory outpatient basis. The drug appears to be of definite value in the control of *petit mal* epilepsy. It appears to be essentially nontoxic.

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Discussion of the Paper

Question: Can you tell us what specific observations led you to the conclusion that meprobamate did not cause any kind of mental retardation or diminution of emotional function in any children whom you treated?

H. R. Litchfield: I can say only that all of our children were outpatient cases, particularly children who were of a more or less normal caliber, and we noticed that they had no particular cloudiness of mentality under the influence of the tranquilizer.

Question: May I ask whether this has been used in cases of enuresis and, if so, what are the results?

H. R. Litchfield: We did not have any cases of enuresis in our series, so I cannot make any definite statements. I think, however, that it should be assumed that, because it might relax these youngsters, they might get some benefit from the medication.

Question: I should like to ask if there has been any maintained improvement after the discontinuance of meprobamate.

H. R. Litchfield: We did find that, once the infant was controlled in early infancy, a very definite decrease of the symptomatology could be maintained. In the older child the discontinuance of the medication caused a return to patterns of undisciplined anxiety, and some of the older boys had the same tension conditions that they had prior to the medication. So I should say that those children under continuous tension, particularly the older group, should be given a maintenance dose of the tranquilizers.

Part IV. Use of Meprobamate in Muscle Spasm

THE VALUE OF MUSCLE RELAXANTS IN DISORDERS OF MUSCLE TONE

By Edward B. Schlesinger
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The neuromuscular abnormalities with which we are concerned manifest themselves clinically chiefly in terms of spasticity or hyperactive stretch response and its sequelae, and rigidity and tremor. The approach lies in an attempt by pharmacological means to ameloriate these mechanisms to a sufficient degree to allow muscle re-education, with a goal of increased motor efficiency in performance and, as a corollary, the prevention of deformity. Such clinical management stands or falls first of all on a complete comprehension of the pathophysiological mechanisms in play. There has been, in the past, a striking lack of communication between groups of workers in the general field concerning their comprehension of various clinical entities. This has been due partly to the use of clinical description without reference to physiological concepts and partly to the fact that the nomenclature was developed by a group of individuals oriented in fields other than neurology. The combination of this type of ambiguous clinical designation, and also the lack of good autopsy correlation, has made a monograph of this kind, involving comparisons of results in similar cases, practically impossible.

To recapitulate briefly, muscular splinting, or spasm, is well defined and may be considered to be a painful reversible contracture of muscle not amenable to voluntary control. Spasticity is chiefly manifested by hyperactive stretch response and is not related to muscular spasm. Rigidity, as in parkinsonism, is a combination of central and peripheral abnormalities and continuing innervation of the peripheral mechanisms. Tremor is likewise a complex entity and may be of various types depending upon the site of pathology. From a pharmacological viewpoint, one can separate these abnormalities into two groups of different complexity of approach, depending upon whether there is a continuing central impress on the peripheral mechanism, or whether this positive central effect is not present.

This clearly divides muscle spasm and spasticity from rigidity and tremor. The former are, as one might predict, easier to influence with drugs. The complexes of central and peripheral origin do not lend themselves to simplicity of therapeutic approach. Why does it seem worthwhile to try to affect these disorders by pharmacological means? Since they have a phasic quality and manifest themselves in terms of altered efficiency of motor function and posture, methods of treatment such as surgery can only resolve the clinical problem by creating a static compromise. A good example of this is the wrist fusion in a case of athetoid posturing, or the diminution of adductor spasticity by nerve section, sacrificing motor strength in an attempt to reduce abnormal stretch response. There are recent notable exceptions to this concept of surgical attack, such as ablation of the presumed centers of abnormal activity.

Pallidectomy for tremor and rigidity is an example of this approach that is in many ways more attractive conceptually than the previously described methods. Short of this latter type of approach, surgery has been, by definition, destructive, with the efficiency of result manifested by reduced motor power in almost exact proportion to the reduction in motor abnormality. Accordingly, the pharmacological approach has certain advantages. Being transient in effect, the drugs can cause no permanent or unalterable change. In this era of rapid advance and understanding of the disease, this is no small attribute in a clinical approach. In broad terms, the goal of the drug method is an attempt to damp the abnormal bombardment of central or peripheral origin. As stated above, depending upon the clinical entity, this can be a simple and theoretically obtainable goal or a very complex problem with no worthwhile answers yet in prospect.

I have touched upon the complexity of this type of investigation in terms of the pathophysiological entities. In addition, there are complexities inherent in the pharmacology of the problem itself. Most drugs have both central and peripheral effects, and these vary in different concentrations. Also, drug effects depend greatly upon the type of pathological process treated. Much misapprehension and many fallacious conclusions have been based on these intricacies of the pharmacological approach. A classic example is curare. Its peripheral effects have long been well known, but its central effects have caused controversy for a long time. Both effects vary greatly with metabolic circumstances and with the nature of the pathology. The effects of curare upon spasticity with partial transection of the cord and complete transection have been proved to be very different, the isolated cord-type spasticity being much more difficult to manage and almost impossible to influence, short of paralysis of muscle.

Further hazard in imputing pure drug effects in clinical studies lies in the constant variation in the clinical study group. All of the abnormal mechanisms we have discussed previously can change from moment to moment in a given patient. I have no desire to belabor the issue, since it is well known and understood by all of us. I should like, however, to underline the variations in response due to factors such as fatigue, the shifting metabolic matrix of the patient, and his prior motor activity. Pain can alter the picture greatly. The emotional climate of the moment has great significance in the patient's total output in response to testing.

One can gather from my comments that I believed clinical testing in this particular field is like grappling with a greased pig. Evaluation of a deep tendon reflexes as a measure of the over-all status of a process such as the degree of spasticity is totally unreliable. By the same token, what we may call more dignified forms of clinical testing, such as electromyography are, in like fashion, unreliable, since the underlying neuromuscular groundwork is constantly changing. Unitary or multiple tests of motor efficiency vary with all the aforementioned considerations, and also, in no small degree, with the patient's transference to his examiner. Somewhere in Reisman's *Individualism Reconsidered*,[1] I was struck by his use of a phrase relating to having a wholesale rather than a retail point of view. This is most applicable here, although in a rather

different connotation. I think a study of the over-all response of these patients is far more rewarding than a meticulous, day-by-day testing of reflex and range of motion. The latter approach can lead only to a realization of the enormous fluctuations in response, fluctuations that are dependent upon innumerable factors that are daily brought to bear upon the patient from both his internal and external environment.

Having done my best to devastate what seems on the surface to be an intelligent means of appraising abnormal muscular disorders, what constructive thoughts can I now contribute to the subject? My group has been through all these phases of attempting to be true scientists in using technical methods to discount human error. Unfortunately we have never been able to achieve any worthwhile conclusions by these means. I should like to acquaint you with what we have arrived at as the best method of testing the effects of drugs in the course of clinical investigation.

Early in the course of our studies at the Institute for the Crippled and Disabled, New York, N. Y., we learned by bitter experience that the medical examiner could not afford to see the patient too often in the course of his treatment. No physician fails to have either a definite positive or negative effect on a patient. This relationship can influence a clinical experiment as a near-by shipload of iron ore affects a compass. One remembers a story of the days when colectomy was done for migraine headache. A famous American physician was making ward rounds in London with the proud proponent of the method. As the two went from bed to bed, the visiting physician heard from the patients nothing but protestations of joy at the quality of the results. Falling behind in one ward, he took advantage of the distance from his host to put a question to the nearest bed patient. "Are you really better," he asked. "Lord love you, no guv'nor," replied the patient, "but I wouldn't hurt his feelings for the world!" The moral is clear; the medical examiner must maintain a flatly critical role in relation to the patient.

The nurse is a most important member of the team. She has a thorough understanding of the drugs under study and the possible complications of their use. She watches carefully for signs of toxicity and is responsible for the blood and urine studies and whatever other laboratory work is necessary. Any comments by the patient fall on sensitive ears when she is about, but she too moves in and out of the picture in a manner calculated to avoid too close rapport with the patient.

The therapists are an extremely vital part of the experimental group and must be selected with care. They must first be taught carefully the terminology of the medical team. It is worth pointing out, although it may seem trite, that the personnel must be secure and must feel that there is an enormous premium on their intellectual honesty. Otherwise, the too-common picture of merely giving what is expected may color the so-called experimental data. The physiotherapists must be allowed to use all their traditional techniques of measuring efficiency of function and range of motion. One should make no attempt to force upon them any terminology except that which will be acceptable to the entire group. The same instructions and admonitions apply to the occupational and the speech therapists.

At the Institute for the Crippled and Disabled we are fortunate in having sufficient staff and support to make the necessary exhaustive patient study. In the course of their stay our patients are seen by psychologists, by social workers, and even by recreational workers. A final critical category of the vocational capacities of each patient is supplied by the vocational supervisor. The patients are put through a battery of vocational tests in order to ascertain their exact motor efficiency and potentialities. Their future training program depends on the results of intergroup consultations among the specialists mentioned above. As the patient filters through this complicated honeycomb of physician, nurse, physiotherapist, occupational therapist, speech therapist, and others, his responses are reported back to the experimental group. During these studies, except for the nurse and the physician, no single individual is aware of what drug is being used or in what concentration. Although I am sure this is far from the best proved means of gleaning experimental data, it avoids many of the pitfalls of more personal methods. If space were not important here, I could recite many fascinating examples of the type of emotional, economic, and physical factors that have influenced patient response in these experiments.

Since 1947 practically every drug with a presumably worthwhile effect on involuntary movement or abnormality in innervation coupled with clinical safety has been used in our studies at the Institute for the Crippled and Disabled. A short list would include atropine and its synthetic derivatives, alcohol in various forms, barbiturates, quinine, *b*-erythroidine, Tridione, Dilantin, Phenergan, Diparcol, Parpanit, curare, Flexin, mephenesin, and its various analogues, Thorazine, reserpine and meprobamate.

Curare, with an obvious myoneural-junction action, has been one of the few drugs with obvious and predictable clinical effects. Unfortunately, these effects are often difficult to control efficiently. Nevertheless, curare remains one of the few drugs with an indisputable action on true spasticity. Its influence on other neuromuscular abnormalities depends completely on whether damping of the myoneuronal junction makes a significant contribution to control. The study of the clinical effects of curare in this general group of disorders gave us many fascinating insights (as did mephenesin) into the nature of some of the entities studied. It would be going off at a tangent, however, to discuss further this particular aspect of our experiment.

Mephenesin, and those of its analogues that we were able to use parenterally, yielded clinical information that could not be discounted as errors of experimental data. There could be no question about the ability of mephenesin to depress hyperactive stretch response, to relieve muscular splinting, and to reduce involuntary movement and rigidity. It is important to qualify these statements by saying that the effects occurred at different concentrations of the drug, and that the responses were of different degree. Also, there was an associated paresis and inco-ordination at the level of efficient effect.

We never found that oral administration of these compounds was sufficient to obtain a clinically worthwhile response. I might add that, occasionally, a patient revealed an extraordinary susceptibility or, perhaps, sensitivity to a compound and made an indelible impression on the experimenter. One of my

earliest mephenesin patients fitted into this category, and perhaps one or two others have done so since then. I cannot dwell on the basis of this uniquely efficient oral response, but I shall say that it was the exception rather than the rule.

Of all the compounds tried—a partial summary of which has been given—Diparcol was the first to give an inkling of the kind of effect under consideration. Shortly after we started to use this drug, three patients spoke to me about its subjective effect. They stated that they performed better because they did not seem to care. It is of interest to note that these individuals were all high-strung and quite intelligent. All were fond of the drug for this reason, although it was hard to determine how motor performance had been altered. The same phenomenon is seen by the student of parkinsonism, whose patients do better because they feel better. Unfortunately, as you know, Diparcol is a difficult drug with which to deal in terms of toxic responses and, regretfully, we had to give it up. I was sufficiently impressed with its potentialities to note in the literature that some drug of the same basic structure could prove most valuable. Eventually, of course, Thorazine answered these requirements to an impressive degree.

The observations of our group with meprobamate were fairly long term and broad. The immediate enthusiasm of the patients in this group alerted us to the possibility that the drug deserved more than a cursory glance. The physical therapists seemed to agree that this was the first available oral preparation with a truly perceptible effect. As the study progressed, it became clear that spasticity was least affected and that the only dramatically altered patients (in the eyes of the therapists) were the athetoids and the dystonics. Here again, as the meaning of our data became apparent, we realized that the good responses were most evident in the highly emotional patients. On final analysis the drug effect seemed to lie in its unique ability to prevent the patient's emotional tension from loading his physical performance. Our continuing observations seemed to confirm rather than unsettle us in this point of view. In careful review of our data, at no time did we see any straightforward drug effect on the basic mechanisms in play such as spasticity or athetoid movement. Nevertheless, the difference in patient performance was often striking.

Over a period of many months we made a careful motion-picture record of patient performance. It was my studied desire to be present neither at the taking of these films nor at their first showings as individual records. There were times when the staff was overwhelmed with enthusiasm over responses. Eventually I was able to go through this voluminous film; it proved to be a dramatic but repetitive example of the progress made by patients treated with various drugs, as already described. It could be seen that the patients were making enormous advances on drugs, and these improvements were perceptible to the most casual onlooker. Even without control films, the conclusions as to the merit of the preparation would be obvious. Unfortunately, the idea that a pictorial record such as a motion picture is necessarily a scientific record is an illusory one.

In conclusion, I have presented a summary of my experiences since 1947 in this field. I have pointed out both the pathophysiological complexity of the

problem and the difficulties of the pharmacological approach, intrinsic in the fact that the drugs themselves are complex. I have dwelt briefly on the variables in the clinical experiment, including the doctor-patient relationship, the natural and wholesome enthusiasm of the clinical experimenter, and the satisfaction derived by the patient who does well. I have outlined what my associates and I consider to be a reasonably adequate technique of study in the screening of drugs. This is far from a scientific approach, but it has seemed to skirt the hazards of many other forms of so-called clinical experimentation. Our experience with this approach has led us to use practically every available drug of reasonable toxicity that has appeared on the horizon in the last ten years. Each of these drugs has afforded us most interesting clinical observations, in many cases providing us with insight into abnormal mechanisms themselves. From a therapeutic standpoint, however, few of the drugs have stood the test of clinical use. We feel that, regarding muscle spasm and spasticity, the quaternary ammonium salts, as exemplified by curare, are the only drugs with definite clinically recognizable direct effect. The substituted ethers of glycerol, as exemplified by mephenesin, are fascinating tools to the neurologist, and they have an unequivocal effect when given intravenously. These effects cannot be maintained practically for long periods by vein, and they cannot be obtained by oral administration. This limits the therapeutic application severely.

Meprobamate has been studied extensively by our group. We continue to feel that it is the first oral preparation that has a real pharmacological action on the athetoid and dystonic group. Short of the creation of drowsiness by its soporific effect, meprobamate seems to insulate the patient's motor performance from the impact of his emotional environment. This leads to a significant and clinically perceptible increase in efficiency of performance. Coupled with its low toxicity, this effect makes meprobamate and its analogues a welcome addition to our armamentarium.

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Discussion of the Paper

QUESTION: You mentioned zoxazolamine (Flexin), which is a new drug in this area. I wonder if you have observed any beneficial effect from its use. It is presumed to be orally effective.

E. B. SCHLESINGER: Our experience with zoxazolamine in the athetotic-dystrophic group was unrewarding. There was some feeling that it afforded some help in dissipating muscle spasm, splinting, and a reduced hyperactive stretch reflex. Long before us, other people at the Medical Center were studying it more extensively than we were. We had an inkling of some liver toxicity, and we discontinued the investigation because the order of therapeutic effect was not sufficient to take chances on the type of toxicity with which we were dealing.

THE USE OF MEPROBAMATE AND OTHER MUSCLE RELAXANTS IN MUSCLE SPASM DUE TO RHEUMATIC CONDITIONS

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The universal rheumatic-symptom complex of aching pain and stiffness (jelling), when occurring alone or in conjunction with some other rheumatic disease has, in general, been considered the cardinal sign of fibrositis. Repeated efforts to discover a consistent pathological picture for fibrositis have met with failure. In fact, the term fibrositis is misleading, since fibrous tissue is not the source of the difficulty and since inflammation cannot be demonstrated. Nevertheless, recognizing the inappropriateness of this term, rheumatologists have accepted it by mutual agreement as designating a condition manifested by aching pain and stiffness occurring with inactivity, relieved by mild activity, salicylates, and/or heat, and recurring with fatigue. The jelling phenomena may occur alone, as primary fibrositis, or in conjunction with some other rheumatic condition, when it is known as secondary fibrositis. In fact, secondary fibrositis is usually found with any rheumatic condition that has a duration of several weeks or longer. Unfortunately, medical as well as lay circles include these symptoms with those of all forms of arthritis, as if they were produced by some unknown element of the articular disease, with the result that treatment programs for the most part contain no therapy directed at the fibrositic involvement. This failure to recognize fibrositis as a separate entity amenable to specific therapy has prolonged the period of disability, has permitted irreparable crippling deformities to occur, and has even led to misdiagnosis in a strikingly large number of patients.

It was difficult to accept the fact that the common-denominator symptoms of jelling resulted from all types of arthritis, regardless of their varied etiology. What abnormality could be present, in primary or secondary fibrositis, to account for these symptoms? Careful examination of the areas of the body involved and careful histories of the events leading up to the onset of the disability, as well as follow-ups when the symptoms have disappeared, reveal the fact that fibrositis is elementally not a disease of fibrous tissue, but is produced by muscle tissue under very definite circumstances.

Fibrositis, whether primary or secondary, is a result of the decrease in muscle strength, bulk, and tone that occurs with muscle atrophy. It may be brought on within several weeks by complete disuse of a muscle(s) or by decreased use over a period of 12 to 24 months, or it may follow postural or other prolonged muscle strain over a period of many years. The atrophy is characterized by a thinning and lengthening of the muscle fibers (elongation of the muscle), a decrease in strength, a delay in stimulus-reaction time, and a loss of tone in the muscles involved. As the atrophy progresses, the muscles tend to develop a "tone" by partial contraction that becomes more pronounced when at rest. This action of the muscle produces the symptom of stiffness and is referred to as "spasm."

It has been found that in the quadriceps muscle these abnormalities can be improved, at least partially, by firm binding with an ace bandage several inches above the knee joint. This takes up the "slack," eliminating the elongation of the muscle and permitting a normal tone to function, making it possible for the existing decreased muscle strength to be more effective.

Fibrositis can be completely cured in a relatively short period of time by regular exercises over and above the daily routine activity, but within the limits of fatigue. Patients have always been handicapped in carrying out rehabilitation programs because of muscle stiffness, weakness, and fatigue. Salicylates, although their use constitutes purely symptomatic therapy, have been helpful. Theoretically, a medication capable of rapidly relieving muscle stiffness without producing paralysis or weakness should permit better function and more rapid rehabilitation. It was not until 1947,[1] when a generally effective muscle-relaxant drug, mephenesin*, was produced for clinical investigation, that this theory could be tested.

Mephenesin proved to be effective in 76.5 per cent of 200 patients with various rheumatic conditions.[2] It was necessary, however, to give a morning loading dose of 0.5 gm. for every 46 lb. of body weight, followed by 0.5 gm. to 0.75 gm. every 3 hours throughout the day. Patients required fewer salicylates with this material and were able to use their muscles to better advantage in a more effective rehabilitation program that was considerably shorter than had been achieved previously with the salicylates. Thereafter, many oral preparations containing mephenesin in combination with other drugs, as well as several without mephenesin, were made available for clinical investigation and, in numerous instances, they were made commercially available for the purpose of relieving the spasm. Many of these preparations were studied in the Benjamin Franklin Clinic prior to commercial release, but none of them proved to have a better effect than mephenesin or its approximately equally effective carbamate†.

Between 1947 and June of 1954, clinical experience in the Benjamin Franklin Clinic indicated that a consideration of the symptoms of fibrositis apart from coexisting arthritis or possible arthritis, with treatment directed at each of the conditions found in a given patient, was much more effective. In fact, many patients who were considered to have the disabling symptoms of such diseases as rheumatoid arthritis, osteoarthritis, or bursitis were made more comfortable or completely overcame their symptoms when the fibrositic elements of the disability were restored to normal by a rehabilitation program in conjunction with salicylates and mephenesin.

Since June of 1954, when meprobamate‡, and later in February of 1955, when zoxazolamine§ investigations were instituted, there has been an increase in the benefit to rheumatic patients from the use of muscle-relaxing medica-

* The generic name for myanesin; provided for clinical investigation as Tolserol by E. R. Squibb & Sons, New York, N. Y.

† Provided for clinical investigation as Tolseram by E. R. Squibb & Sons, New York, N. Y.

‡ Provided for clinical investigation as Miltown by Wallace Laboratories, New Brunswick, N. J.

§ Provided for clinical investigation as Flexin by McNeil Laboratories, Philadelphia, Pa.

tions. Both meprobamate and zoxazolamine have been found superior to mephenesin and its carbamate.

Meprobamate, 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate, is a dicarbamate derivative of mephenesin.[3] It is characterized by three pharmacological properties: a muscle-relaxant action, an anticonvulsant action, and a taming effect that can be seen best in monkeys. It has a specific blocking action on interneurons, but it does not affect any of the reflex arcs that contain no interneurons. This is the action that produces muscle relaxation. Another interesting property is its action upon the thalamus where, by electrical recordings, it can be shown that in therapeutic doses there is a marked synchronization of the activity, as indicated by a slowing of the frequency and a distinct increase in the voltage.[4]

Zoxazolamine, 2-amino-5-chlorobenzoxazole, is most closely related to benzimidazole, which was at one time thought to have antiviral activity. This preparation was developed and characterized by the research group of McNeil Laboratories, Philadelphia, Pa. It produces a depression of the polysynaptic pathways.[5a, 5b] The clinical investigation of neuromuscular structures showed a central action for zoxazolamine with essentially no effect upon the muscle, the myoneural junction, the monosynaptic pathways, or the motor nerves. The pharmacological action produces a relaxation of the spasm of striate muscles by a depression of the central nerve pathways.

Meprobamate has been available as a compressed, scored, 400-mg. tablet. The dosage consists primarily of 400 mg. 4 times a day, but occasionally some patients achieve adequate muscle relaxation with only 400 mg. 3 times a day, and some with 200 mg. 4 times a day. Although a 500-mg., scored tablet of zoxazolamine was first used for clinical investigation, this drug has thus far been available in the 250-mg. form only. Both an uncoated and an "engestic" coated tablet are manufactured, however. The dosage recommended is 250 or 500 mg. 4 times a day with the compressed tablet or, if gastric irritation develops, the enteric coated tablet in the same dosage may be used. The enteric coating has an average disintegration time of 3 to 4 hours.

Response to Therapy

The response to therapy was considered excellent when there was evidence of muscle relaxation within 20 to 30 min. after the tablet was ingested and when this relaxation continued throughout the day on a normal dosage schedule. A good response occurred when only minimal stiffness or aching persisted beyond 30 to 60 min. after administration of the drug. In 2 groups of 96 patients treated with these 2 muscle-relaxing drugs the therapeutic effectiveness was essentially the same, with an over-all improvement of 86.4 per cent for meprobamate and 88.5 per cent for zoxazolamine (TABLE 1).[6] There was 100 per cent benefit in the treatment of acute torticollis, muscle spasm of the low back, and osteoarthritis of the hip. Further experience with less careful selection of patients, that is, when muscle spasm had existed over a longer period of time or when the osteoarthritis of the hip was also producing symptoms, proved that the 100 per cent response was greater than had been expected.

TABLE 1
COMPARISON OF MEPROBAMATE AND ZOXAZOLAMINE

Disease	No. of patients		Patients benefited	
	Mep.	Zox.	Patients / per cent mep.	Patients / per cent zox.
Rheumatoid spondylitis	21	16	19 / 90.4	15 / 93.7
Fibrositis	20	34	17 / 85.0	30 / 88.2
Cervical root syndrome	27	22	23 / 85.2	19 / 86.8
Rheumatoid arthritis, mild	17	18	13 / 76.5	15 / 83.3
Torticollis, acute	4	2	4 / 100.0	2 / 100.0
Muscle spasm of the low back	3	3	3 / 100.0	3 / 100.0
Osteoarthritis of the hip	4	1	4 / 100.0	1 / 100.0
	96	96		

Total benefit: meprobamate, 86.4; zoxazolamine, 88.5.

The utility of these drugs was demonstrated to be superior to mephenesin preparations in rheumatoid spondylitis, fibrositis, cervical root syndrome, and mild rheumatoid arthritis. There was a longer duration of action, as shown by the efficacy of 3 or 4 doses per day, as well as by a greater percentage of improvement.

Toxic Effects

The comparison of the toxic effects caused by meprobamate and zoxazolamine is very interesting (TABLE 2).[6] There were 9 different reactions with meprobamate therapy and 10 with zoxazolamine. The reactions most commonly seen with one drug were of a different nature than those with the other.

Meprobamate produced drowsiness in 48 patients. This finding was controlled—by continuation of the same dosage in 21, by decreasing the dosage by 50 per cent in 12, and by discontinuation in the remaining 15. The other most common side effect was sluggishness of the bowel, which was akin to that seen in some patients with salicylate or ferrous sulfate therapy. This effect was overcome in 6 patients with a reduction of the dosage of medication, and discontinuance was required in only 2. Each of the other toxic effects was found in only one patient. Nausea disappeared when the dosage was reduced by 50 per cent. On the other hand, nausea and vomiting, overstimulation, exhaustion, ulcer symptoms, and rash were considered severe enough for discontinuance of therapy. None of these side effects for which therapy was discontinued persisted after the drug was stopped. It was deemed essential to return the patient who had a recurrence of his ulcer symptoms to his anti-

Table 2

Toxicity of Meprobamate and Zoxazolamine

Effect	No. of side effects		Cleared on same dose		Cleared on 50% dose	
	Mep.	Zox.	Mep.	Zox.	Mep.	Zox.
Drowsiness	48	3	21	0	12	2
Nausea	1	12	0	3	1	7
Nausea & vomiting	1	0	0	—	0	—
Dizziness	0	11	—	4	—	5
Sluggish bowel	8	0	0	—	6	—
Epigastric burning	0	4	—	0	—	2
Lightheadedness	0	5	—	2	—	3
Overstimulation	1	4	0	0	0	2
Depression	0	1	—	0	—	0
Exhaustion	1	0	0	—	0	—
Ulcer symptoms	1	0	0	—	0	—
Rash	1	1	0	0	0	0
Chills & fever	0	1	—	0	—	0
Burning & tearing of the eyes	0	1	—	0	—	0
Total	62	43	21	9	19	22

ulcer program for a week, and the patient with the rash received local hydrocortisone ointments for several days. None of the patients on meprobamate experienced dizziness, epigastric burning, lightheadedness, depression, chills and fever, or burning and tearing of the eyes. Thus far we have seen no evidence of purpura hemorrhagica, as reported by Gottlieb.[7] Lemere[8] reported evidence of habit formation in several alcoholic patients, as well as a need for increasingly larger doses in several cases. This has not been observed in our experience.

The most common findings in the patients receiving zoxazolamine were nausea, dizziness, lightheadedness, epigastric burning, overstimulation, and drowsiness, in that order of frequency. Nausea required cessation of therapy in only 2 patients; it disappeared with continuation of the same dose in 3 instances and cleared with decrease of the dosage by 50 per cent in 7. Mild dizziness also cleared in 4 of the 11 patients with no change in dosage; it was no longer a problem in 5 cases after the medication was decreased by 50 per cent, and it necessitated discontinuance in only 2 patients. There was no need to withdraw the medication for lightheadedness, since 2 patients overcame this effect without changing medication, and 3 overcame it with the decreased dosage. The cases of epigastric burning and overstimulation were severe enough to necessitate discontinuance in 2 instances, and they cleared in 2 others with lowered dose. In addition to these side effects, depression, rash, chills and fever, and burning and tearing of the eyes each occurred in 1 patient. The symptoms were considered sufficiently severe in each of these 4 instances to discontinue the medication. These side effects cleared rapidly thereafter. There were only 3 patients who complained of drowsiness with zoxazolamine therapy. This improved after a decrease of dosage in 2 cases, and it persisted severely enough for discontinuance of therapy in 1.

Kron[9] has reported a patient who developed urticaria with meprobamate and who exhibited a probable sensitivity to all members of the mephenesin family. Approximately 9 months ago, within 24 hours after starting therapy with mephenesin carbamate, this patient developed a generalized urticaria that responded in 72 hours to withdrawal of the drug and local treatment with hydrocortisone lotion. Eight months later she developed another rash. She admitted taking 1 meprobamate tablet the night before to induce sleep. The tablets had been prescribed for her husband. Friedman and Marmelzat[10] currently report 5 patients who took 1 to 4 tablets and developed a rash, and 2 patient who took 1 and 4 tablets for 7 and 15 days, respectively, with the same result. These cases confirmed sensitivity to meprobamate, but Friedman and Marmelzat did not report previous experiences with compounds chemically related to meprobamate. The possibility of this type of related sensitivity should be considered in prescribing meprobamate.

Comparisons of the toxic effects with these 2 medications showed 62 patients involved with meprobamate and 43 with zoxazolamine. Therapy was discontinued in only 22 patients on the former and 13 patients on the latter drug. In this series there was a ratio of 13.5 per cent toxicity to zoxazolamine and 23 per cent toxicity to meprobamate. In the latter instance, however, two thirds of the side effects were due to drowsiness, which has been found to be useful in the treatment of many patients.

The side effect of drowsiness has utility in the rheumatic-disease field, where overactivity, tension, and nervousness are present. This type of patient responds very well. Some may experience slight drowsiness, but most are only slowed to a more normal pace. It is important, however, to bear in mind that those who drive their own cars should be warned to be cautious until it is determined whether or not they will react with drowsiness to the drug.

The soporific effect of meprobamate was used to good effect in many patients who had difficulty sleeping because of such states as hyperexcitability, agitation, and nervousness. Many of these patients, on normal doses of 400 mg. 4 times a day, found that they were finally able to have a restful sleep. In other instances, 1 tablet at bedtime did not seem to be sufficient and was increased to 2 tablets. It was reported frequently by patients receiving 2 tablets, as well as by some of those receiving only 1 tablet at bedtime, that they apparently did not move from the position in which they fell asleep, a complete reversal of their previous experience. If stiffness had been slightly increased by this absolute inactivity during the night, it was quickly relieved by the morning dose of meprobamate or by an additional dose of 250 to 500 mg. of engestic-coated zoxazolamine at bedtime for its delayed action. An ever-increasing number of patients who required occasional or frequent bedtime sedation have discovered that meprobamate is an excellent substitute for barbiturates, inducing restful sleep without a "hangover."

Clinical Use

The question has frequently been raised in discussions of these newest muscle-relaxing preparations as to which one is preferred. Essentially, they are equal in their utility, but they lend themselves to a paired action with a proper

selection of patients. To date, no patient has exhibited intolerance or refractiveness to both drugs. In some patients it would be undesirable to use only one of these drugs.

The choice of preparation for a given patient is dependent primarily upon the pharmacological actions of the drug, as well as upon the tolerance of the patient. In general, the choices are as follows:

(1) The tense, nervous, fearful, hyperactive type of rheumatic patient generally does well on meprobamate, 400 mg. 4 times a day.

(2) The depressed, slow-moving, relatively inactive rheumatic patient responds better to zoxazolamine, 250 to 500 mg. 4 times a day.

(3) Those patients cited in group No. 2 who had difficulty sleeping when taking zoxazolamine 4 times a day, may be given, instead, zoxazolamine 3 times a day before or after meals, with 1 or 2 tablets of meprobamate at bedtime.

(4) If zoxazolamine causes overstimulation it may be better to give alternate doses of this drug and meprobamate, starting the day with the former and ending with the latter.

(5) For a soporific effect, in patients with or without rheumatic diseases, 400 mg. to 800 mg. of meprobamate should be given before retiring. Patients who require intermittent or even fairly regular bedtime sedation have responded well to meprobamate instead.

(6) The use of either one of these newest preparations for the treatment of the symptoms of acute fibrositis can prevent numerous patients from overresting and developing more muscle atrophy and a chronic fibrositis. Medication for the acute phase is seldom needed longer than a few days to a week. At the same time, patients should be encouraged to carry on their activities as normally as possible to prevent any undue atrophy.

Table 3 shows the distribution of 325 patients with various rheumatic conditions, and the choice of therapy with meprobamate, zoxazolamine, or a combination of the two. The therapy was changed from one form to another in 174 patients because of mild side effects, including drowsiness, nausea, dizziness, lightheadedness, sluggish bowel, and overstimulation. No toxicity to both preparations was exhibited in a given patient. The group with osteoarthritis deserve special comment. This diagnosis had been made previously in each of the 36 patients and had been "confirmed" by X ray. However, as so often happens, the only symptoms complained of were those of fibrositis. Physical examination revealed atrophy and weakness of the muscles of the involved areas. In spite of the roentgenographic findings, the symptoms were relieved with muscle-relaxing medication and cleared completely with the addition of a successful rehabilitation program. It is to be presumed that such developments as spurs and narrowing of joint spaces were normal aging changes in these patients, and not osteoarthritis.

Δ-Steroids and Meprobamate

Since a number of our rheumatoid arthritic patients receiving Δ-steroids complained of excitability, nervousness, and inability to sleep at night, my colleagues and I determined to test the compatibility and the reaction of con-

TABLE 3

MUSCLE-RELAXING THERAPY IN RHEUMATIC DISEASES: DISTRIBUTION OF PATIENTS

Disease	No. of patients	Patients benefited: number / per cent		
		Meprobamate	Zoxazolamine	Combined
Fibrositis	108	62 / 57.4	31 / 28.7	15 / 13.8
Cervical root syndrome	52	18 / 34.6	19 / 36.5	15 / 28.8
Rheumatoid spondylitis	32	17 / 53.1	8 / 25.0	7 / 21.8
Rheumatoid arthritis, mild	47	29 / 61.7	12 / 25.5	6 / 12.7
Muscle spasm of the low back	31	16 / 51.6	15 / 48.4	0 / 0
Osteoarthritis	36	20 / 55.5	12 / 33.3	4 / 11.1
Torticollis	19	11 / 57.9	7 / 36.8	1 / 5.2
Total	325	173 / 53.2	104 / 32.0	48 / 14.7

comitant Δ-steroid and meprobamate therapy. We were provided with a tablet containing 2.5 mg. of prednisolone and 200 mg. of the muscle relaxant*. We found that this preparation very effectively offset the overstimulation of the steroid, although we were handicapped to a considerable degree by the difficulty in regulating dosage levels with this size tablet while, at the same time, maintaining adequate meprobamate therapy. In many instances we had to add additional meprobamate when the combination tablet was broken in half to reduce the dosage of steroid. Since then we have had available two capsules, one containing 1 mg. of prednisolone with 200 mg. of meprobamate, and the other containing 2 mg. of prednisolone with 200 mg. of meprobamate†. Later we had multiple compressed tablets in the 2 strengths plus 200 mg. of aluminum hydroxide‡ in each. These 2 dosage forms made it possible to provide 8 mg. to 16 mg. per day of the steroid without excessive amounts of the muscle-relaxant drug or without the need to give additional meprobamate (FIGURE 1). The schedules for the administration of these capsules to provide various amounts of the prednisolone per day are well illustrated in FIGURE 1. A combination of a plain white tablet and one containing a symbol simplified the instructions to the patient, particularly when it was desirable to alter the steroid dosage. It was our opinion that this type of combination therapy was simple and better able to effect the results desired. There were no toxic effects in this group of patients.

* Supplied for clinical investigation by Wallace Laboratories, New Brunswick, N. J.

† Supplied for clinical investigation by Merck Sharp & Dohme Research Laboratories, West Point, Pa.

‡ Supplied as Meprolone by Merck Sharp & Dohme Research Laboratories, West Point, Pa.

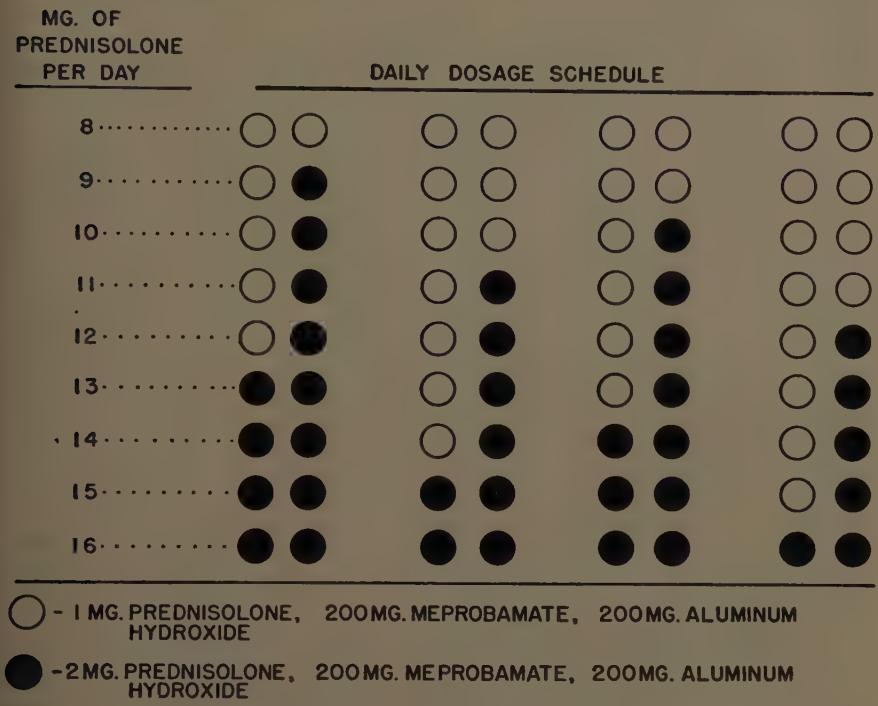


FIGURE 1. Meprolone dosage schedule.

In previous reports[6, 11, 12] it has been emphasized that the muscle-relaxing drugs have been effective in rheumatoid arthritis when the joint activity has been minimal and the fibrositic symptoms have predominated. The use of the combination tablets of Meprolone permits the control of symptoms of moderate to severe rheumatoid arthritis without using excessive amounts of steroid. It has been frequently observed that, while reducing prednisolone stepwise to reach a minimal maintenance level of the steroid in patients with rheumatoid arthritis, a dosage will be reached where the patient complains bitterly of discomfort, although the joints are quiescent. An additional 2 to 5 mg. of prednisolone may be required to make the patient comfortable. The symptoms causing the complaint can be readily identified as the aching and stiffness of fibrositis. Meprolone has been found to be effective in these patients, since the fibrositic symptoms can be relieved, while the lowest possible maintenance level of the prednisolone can be determined by gradual 1-mg. alterations in dosage. The undesirable side effects of steroid therapy are less likely to appear with the administration of the lowest possible quantity of prednisolone. Even during the initial stage of therapy, when higher steroid dosage may be required for suppression of the arthritis, excessive stimulation, excitability, and sleeplessness can be overcome. It is possible that during the early phase of suppressive therapy additional Meprolone may be given before retiring or during the night, as required. In general, however, up to 16 mg. of

TABLE 4
MEPROLONE IN RHEUMATIC DISEASES

Diagnosis	No. of patients	Previous prednisolone therapy, mg.	Meprolone per day No. of patients			
			Steroid		Meprobamate	
			Same	Reduced	1600 mg.	800 mg.
Rheumatoid arthritis						
Mild	17	10.0	4	5	7	2
		12.5	2	6	8	0
Moderate	11	12.5	1	2	3	0
		15.0	2	6	7	1*
Severe	9	20.0	3*	3†	6	0
		25.0	0	3‡	3	
Psoriatic arthritis	1	10.0	0	1	1	0
Palindromic rheumatism	2	10.0	0	2	1	1
Rheumatoid spondylitis	6	10.0	1	3	4	0
		12.5	1	1	1	1
Lupus erythematosus	1	15.0	0	1	1	0
Scleroderma	3	12.5	2	0	2	0
		15.0	0	1	1	0
Total	50		16	34	45	5

* Supplemental prednisolone: 5.0 mg.
† Supplemental prednisolone: 2.5 mg.
‡ Supplemental prednisolone: 7.5 mg.

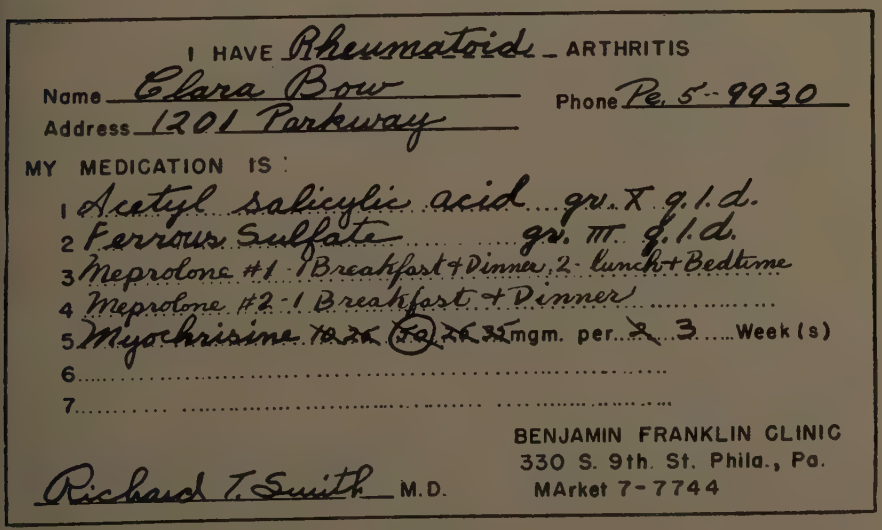
prednisolone can be provided by the Meprolone and supplemental steroid; usually 2.5-mg. tablets should be administered for higher levels.

The program of treatment generally planned for a patient with active rheumatoid arthritis or its variants of psoriatic arthritis, palindromic rheumatism, and episodic rheumatoid arthritis consisted of Meprolone sufficient to control symptoms with or without salicylates, gold therapy,[13, 14] and rehabilitation exercises. Other therapy, such as the administration of iron salts and intra-articular injections, was prescribed as necessary. The maintenance level of Meprolone was achieved as soon as possible. As the gold therapy became effective the steroid dosage was reduced gradually and was finally discontinued. Rheumatoid spondylitis was treated in the same manner, except that roentgen therapy was prescribed instead of gold.

A summary of experience with Meprolone therapy in 50 patients with various collagen diseases is given in TABLE 4. Thirty-four patients were well maintained on a lower daily dose of prednisolone (1.0 mg. to 2.5 mg. less) on the combination therapy. Due to excessive drowsiness, in 5 instances the meprobamate dosage was reduced to 800 mg. per day. One of these 5 patients, with moderate rheumatoid arthritis, who had been receiving 15 mg. of prednisolone per day, required 5 mg. of supplemental steroid for adequate control, but this total dose was only 13 mg., a reduction of 2 mg. The 9 patients with severe rheumatoid arthritis, who had been maintained on 20 to 25 mg. of prednisolone daily, were given 2.5 mg. to 7.5 mg. of supplemental steroid. Nevertheless, the total dose was reduced in 6 of the 9. No toxic effects were seen in these patients.

At the Benjamin Franklin Clinic we have found it possible to administer smaller doses of steroids if the patients were not aware that they were taking "miracle drugs." To establish this theory we have provided them with various types of combination tablets containing steroids designated by our own terminology. In other words, a patient with rheumatoid arthritis who has been receiving salicylates but no steroid therapy will be much improved when no more than 40 mg. of hydrocortisone or no more than 12.5 mg. to 15 mg. of prednisolone or prednisone is added. He will have a greater relief from discomfort and will be able to perform activities and motions of which he was incapable previously. If the patient is aware that a "miracle drug" is being administered, he demands the complete relief of symptoms described thoroughly in lay literature. In rheumatoid arthritis this program of steroid therapy is combined, of course, with the inauguration of gold therapy. When the gold therapy begins to show benefit, the steroid dosage is decreased stepwise (never more than 2.5 mg. every 5 days or longer) and, finally, it is discontinued.

We realize many physicians believe that, because of the medical or surgical emergencies which may arise, patients should be told they are taking steroids. The steroid dosage can be obscured among the other medications with a pocket card that the patient carries at all times. An example of this card is shown in FIGURE 2. Here the patient's diagnosis and his name, address, and telephone number are filled in on a printed form. All the medications the patient is receiving are shown. At the bottom are the physician's name or signature and his address and telephone number. Many of the various medications listed are familiar to the patient, but others, when inquired about, can be described in an offhand fashion. The patient should be instructed to present this card if he is ever in an accident or is hospitalized for any cause, or if, for any reason, he should need additional medical care.


I HAVE Rheumatoid ARTHRITIS

Name Clara Bow Phone Pe. 5-9930

Address 1201 Parkway

MY MEDICATION IS:

1 Acetyl salicylic acid gr. X q.i.d.

2 Ferrous Sulfate gr. III. q.i.d.

3 Meprolone #1 - Breakfast + Dinner, 2 - lunch + Bedtime

4 Meprolone #2 - 1 Breakfast + Dinner

5 Myochrisine 10 25 50 mgm. per 2 3 Week(s)

6

7

BENJAMIN FRANKLIN CLINIC
330 S. 9th. St. Phila., Pa.
MArket 7-7744

Richard T. Smith M.D.

FIGURE 2

Comment

The discovery of Myanesin opened an entirely new approach to the therapy of the rheumatic diseases. Stemming from this preparation, interest has been stimulated in the search for better muscle-relaxing drugs that will not produce paralysis or weakness in muscles relieved of spasm. This is, of course, only symptomatic therapy but, unlike salicylates, which only relieve pain, the muscle spasm is overcome through its application and the cause of the pain is removed, thereby permitting the patient to enter into a program of rehabilitation with greater ease. Unless a program of muscle rebuilding is instituted, symptomatic therapy is required for extremely long periods of time, with the possibility that the cause of the symptomatology may never be completely overcome. The use of meprobamate and zoxazolamine, the newest and best drugs for the production of muscle relaxation, presents a new high in this type of therapy.

Fibrositis, tardily recognized as a specific entity in the United States, is now rapidly increasing. The trend is toward less and less physical activity through greater use of wheels. More and more drive-in facilities are available; one need no longer get out of one's car to go to the bank; there are golf-mobiles to take the tired golfer from tee to tee; entertainment in the home is now possible by merely seating oneself in front of a television set for an entire evening. This increased inactivity is developing more and more gradual muscle atrophy and fibrositis, the first signs of which, to the layman, are indicative of a need for more rest, with a resultant production of greater atrophy and symptoms and a prolongation of the discomfort. Several outstanding football coaches and college trainers recently agreed that ten years ago it was necessary to spend several weeks loosening up the well-developed lower-extremity muscles of football players. Now a month is required to *build* muscles in order that injuries will not occur to the knees of these athletes. One coach pointed out that the men get even less exercise than formerly when driving a car, since now they have no clutch pedal to press. This is just another sign of the times. Unless the medical profession realizes the gravity of this situation and educates the public against the trend toward less and less physical activity, the results may be disastrous to the nation.

In chronic fibrositis the patient must be impressed with the need for rehabilitation. The necessity for therapeutic exercise may be more striking if it is explained that this condition requires muscle rebuilding, and the proof of this need can be shown by the muscle-relaxing effect of either meprobamate or zoxazolamine. When the desired effect has been achieved and, as predicted, stiffness is relieved, co-operation in a self-help program is almost assured.

It is most unfortunate that a stigma has been attached to the muscle-relaxing drugs by the unfortunate and incomplete reporting of their use in the lay literature.[15, 16] Diagnoses of psychoneurosis continue in ill repute with a large portion of the laity. When the weekly news journals, the newspaper columns, and the jokes of popular comedians, all stress the use of a popular drug for the relief of neurotic symptoms, the layman receives the impression that it is of value only for this purpose. This opinion is so common that many patients

have discontinued medication and changed doctors because they thought they were being hoodwinked when they were told that the prescription was for muscle relaxation. The utility of these drugs in the rheumatic-disease field suggests that their greatest activity is that of muscle relaxation, and this action, more than any other, brings about the relief of tension and the calming effect that is so popularly sought. Large numbers of people have never learned how to relax. Now, for the first time, they find relief from tense, tight muscles and, consequently, from their tension states. It is hoped that the presentation and publication of articles concerned with the use of muscle-relaxing drugs will promote better understanding of their use and thus a better acceptance of them by patients.

Belief that muscle relaxation is probably the action that produces the calming effect is further supported by the fact that zoxazolamine produces very little drowsiness and is also a source of relief to patients with tension states. This type of activity differs from that of the ataractic or tranquilizing drugs. It is suggested that meprobamate and zoxazolamine are improperly classified as ataractics. Possibly there is a distinct difference in the types of action at different dosage levels. At the levels recommended in this paper, a more descriptive term[17] might be "lissive agents*."

Previous reports[7, 11, 12] of studies with meprobamate and zoxazolamine at the Benjamin Franklin Clinic have indicated beneficial effects in patients with mild rheumatoid arthritis in which the aching and stiffness of fibrositis predominated symptomatically, while the response in moderate to severe forms of the disease was disappointing. The combination of 200 mg. of meprobamate in a tablet with 1 or 2 mg. of prednisolone, on the other hand, has been very encouraging in moderate and severe forms of the collagen diseases. Meprolone in 2 strengths permits the administration of a constant dose of meprobamate while the steroid dosage can be varied by 1-mg. increments between 8 and 16 mg. The use of this type of medication tends to correct the undesirable practice of giving more prednisolone than is required for control of the joint symptoms. Thirty-four of 50 patients were controlled with smaller doses of steroid when meprobamate was administered concomitantly. In addition, the overstimulation of the patients was relieved. Lower and safer doses of steroids can be administered if the patients are not aware that they are receiving a "miracle drug."

Conclusions

Meprobamate and zoxazolamine are unrelated chemical compounds having the ability to produce muscle relaxation. They are essentially equal in their utility, and they complement, rather than compete with, each other. There has been no evidence of serious toxicity with either preparation in this series of patients. Some of the side effects can be used to good advantage. In particular, the tendency to drowsiness may be used to slow down hyperactive patients, while the lack of soporific effect exerted by zoxazolamine may be used in patients who tend to be depressed and inactive. Approximately two thirds

* Reduction of excessive skeletal muscle tone (spasm), without production of paralysis.

of the toxic effects occasioned by each medication can be overcome by reducing the dosage by 50 per cent. Only activation of ulcer symptoms, rash, chills and fever, burning and tearing of the eyes, and depression have proved serious enough to necessitate immediate discontinuation of therapy. These compounds do not fit properly into the classification of ataractics, but are better described as "lissive" agents. Meprobamate and zoxazolamine are the best muscle-relaxant drugs that have been made available to date. Therapy with them should be individualized, and the choice of one or the other should depend upon the type of patient to be treated. When desired, these two drugs may be used as companions, with no evidence of incompatibility. The combination of meprobamate and prednisolone in tablets containing 1 or 2 mg. of the steroid provides a flexible dose of the latter, while maintaining a constant level of the former. The majority of patients studied with this new form of medication required less steroid than they had previously needed.

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THE USE OF MEPROBAMATE IN THE TREATMENT OF SKELETAL MUSCLE SPASM

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Since the introduction of chemical agents for the relaxation of spastic skeletal muscle, investigators have sought a form of oral medication that would be effective, nontoxic, and of reasonably long duration. In 1946, Berger and Bradley[1] introduced mephenesin, an interneuronal blocking agent that produced relaxation of skeletal muscle without impairment of muscle function. Although promising results were obtained in some cases,[2-4] the low activity of the drug and the necessity for intravenous administration seriously limited its clinical usefulness.

Meprobamate (Miltown*), which has pronounced muscle-relaxing properties and greatly prolonged duration of action, has more recently been introduced by Berger.[5] Its development followed the observation that the short duration of action of mephenesin was due to the rapid oxidation of its primary hydroxyl group.[6] When this radical was blocked and when carbamic-acid groups were introduced, greater duration of activity resulted. Meprobamate (2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate) showed the most pronounced muscle-relaxing properties.[5] Paralysis lasting for 3 to 4 hours with muscle impairment for about 24 hours was produced in cats by intraperitoneal, 100-mg./kg. injections of the drug. A similar dose of mephenesin produced paralysis for only about 15 minutes, and all signs of muscular impairment disappeared after 1 hour. The oral paralyzing dose of meprobamate was only slightly higher than the parenteral.[7]

Like mephenesin, meprobamate is an interneuronal blocking agent. The drug acts on the central nervous system only. It does not act on involuntary muscle, the myoneural junction, or peripheral nerve, and it does not affect the autonomic functions.[5] Unlike mephenesin, meprobamate produces a pronounced effect on subcortical structures. Monkeys became tame after the administration of meprobamate, and electroencephalogram records taken from the cat showed synchronization of the brain waves recorded from the thalamus.[8] Clinical studies to date have dealt chiefly with this tranquilizing effect of the drug.[9-11]

Pharmacological studies proved meprobamate to possess extremely low toxicity, to have no harmful effect on blood, liver, or kidney function, and to have no depressant action on blood pressure or respiration.[5] Clinical results have confirmed these observations.[9-11]

Berger and Ludwig[12] found that about 10 per cent of the product is excreted unchanged in the urine. Since none of the metabolic products of 2-methyl-2-*n*-propyl-1,3-propanediol were found in the urine, it is assumed that the propanediol entity is not disassociated from the carbamate groups in passage

* The meprobamate (Miltown) used in this study was supplied by Wallace Laboratories, New Brunswick, N. J.

through the body. A large portion of meprobamate, or some breakdown product of the drug, is probably conjugated in the body to a glucuronide, or a similar type of compound, and is excreted from the body in conjugated form for about 24 hours following ingestion.

Clinical Evaluation

We began a clinical evaluation of meprobamate in 1954. The study was conducted on private patients at the Central Dispensary and Emergency Hospital, Washington, D. C., at Prince Georges General Hospital, Cheverly, Md., and in ambulatory office patients. Many of the patients had conditions that would have responded to cortisone or cortisonelike preparations, but we preferred to use a drug with fewer side effects. Initially, the drug was given to patients with acute torticollis, or "stiff neck," and acute low back strains. The study was then widened to include patients with skeletal muscle spasm, irrespective of its cause. Prior to this study patients with similar conditions were given medications that had either a curare or a prostigminelike effect. The results from the administration of these drugs were not too satisfactory.

Scope of the study. The patients whose records are included here had one or more of such conditions as muscle spasm, pain and tenderness, restriction of motion, or shift of trunk. Both acute and chronic cases were included, and all adult age groups were represented.

One hundred and fourteen patients were treated with meprobamate, including 7 who could not be evaluated. Two of these unevaluated patients displayed sensitivity and were taken off the drug. The remaining 5 presented psychological problems such as refusal to obey instructions, temporary alleviation of symptoms following any medication, or persistence of pain without objective causes, all of which would have made the validity of evaluation doubtful. These cases have been excluded from the tabulations of results; the final evaluations include 107 patients.

Dosage. At the beginning all patients were given two 400-mg. meprobamate tablets four times daily for 2 days and then were decreased to 1 tablet three times a day, with 2 tablets at night. This dosage produced drowsiness in too many patients during the first 2 days. The reduced dose schedule was purposely arranged so that the dose prior to bedtime would act as a soporific, thus eliminating the need for a barbiturate. The dosage finally determined for ambulatory patients was 1 tablet three times a day, with 2 tablets 30 min. before retiring. At this level the drug was well tolerated by all but a few patients in whom drowsiness persisted; however, this could be relieved by the administration of 2.5 mg. of any amphetamine compound for each 400 mg. of meprobamate. Hospitalized patients were continued on the dose of 2 tablets 4 times daily, since sleepiness is not harmful under these conditions and may be an adjuvant to therapeutic success. Relaxation could be achieved somewhat more rapidly at the higher dose than at the lower.

Some effect of the medication was usually experienced within 24 hours. Patients with acute muscular spastic conditions were maintained on meprobamate usually for 7 days, by which time objective evidence of spasticity was generally relieved. In these instances, in which the medicine was used to alleviate the

spastic element associated with chronic conditions, patients were permitted to take the drug for many months. On occasion it was administered for over a year. Toxicity was not apparent, and the effectiveness was maintained.

Since all patients included in this study were private patients, they necessarily received, in addition to meprobamate, the established and accepted treatments for their specific conditions. In all the cases with a favorable response, improvement was achieved in a shorter period of time than had been noted under conventional therapy prior to the use of meprobamate.

Clinical Results

Results were evaluated both by symptom and by diagnosis, according to the following criteria: (1) remission of symptoms was complete, or nearly complete —classified as "recovered"; (2) symptoms were greatly, but not completely, relieved—classified as "marked improvement"; (3) symptoms were significantly, but not strikingly, relieved—classified as "some improvement"; and (4) symptoms were not relieved, or were only slightly relieved—classified as "no improvement."

Table 1 shows the results of treatment of various conditions. Of the 107 patients included in the study, 90 per cent were significantly improved, 65 per cent showing marked improvement or complete recovery.

Acute and chronic low back strains accounted for approximately half the diagnoses. While nearly all patients in both these groups showed some benefit from meprobamate, those suffering from acute strain showed greater improvement (73 per cent recovered or were markedly relieved) than those suffering from chronic strain (58 per cent recovered or were markedly relieved).

The greatest specific improvement in any one condition occurred in acute cervical myositis. Of the 24 cases considered in this report, all but 2 showed complete recovery or marked improvement. In a previous study, conducted by Neviaser[13] with only the use of cervical traction, a favorable response in

Table 1

Results of Treating 107 Patients with Meprobamate: by Diagnosis (Evaluation of Symptomatic Relief Only)

Diagnosis	Total cases	Degree of improvement				Per cent improved	
		Recovered	Marked	Some	None	Recovered or marked improvement	Some improvement
Acute low back strain	19	4	10	5		73.7	100.0
Chronic low back strain	36	3	18	12	3	58.3	91.6
Acute myositis of cervical spine (wry neck)	24	8	14	1	1	91.7	95.8
Osteoarthritis	9	2	4	3		66.6	100.0
Protruded intervertebral disc	12	1	4	3	4	41.7	66.6
Postoperative conditions	7	1	1	3	2	28.6	71.4
Miscellaneous	2	1		1			
Total	109*	20	51	28	10	65.1	90.8

* Two patients presented double diagnoses, making a total of 109 cases.

TABLE 2
RESULTS OF TREATMENT WITH MEPROBAMATE: BY SYMPTOM

Symptom	Total instances	Degree of improvement				Per cent improved	
		Symptom-free	Marked	Some	None	Symptom-free or marked improvement	Some improvement
Pain and tenderness	107	19	49	29	10	63.6	90.7
Muscle spasm	87	15	43	22	7	66.6	92.0
Limitation of motion	82	7	38	28	9	54.9	89.0
Shift of trunk	5		2	3		40.0	100.0
Total	281	41	132	82	26	61.6	90.7

acute cases was usually noted in 72 hours. In the present study, improvement with meprobamate was evident in a shorter time.

Spasm associated with extensive osteoarthritis of the spine also responded favorably. All 9 cases under treatment were significantly improved, and over 65 per cent showed marked improvement or recovery from an acute spastic episode.

Spasticity and pain related to protruded intervertebral discs and postoperative conditions appeared to respond less well to treatment. In the cases of disc protrusions, surgery was often required, but was either being refused or postponed to a more opportune time. Meanwhile, meprobamate was given to relieve pain and discomfort. The number of cases treated in this fashion was relatively small. It would be necessary to consider many more cases of this type before definite conclusions could be drawn as to the efficacy of the medication in these patients.

TABLE 2 shows the results of the study by symptoms. In 107 instances of pain and tenderness and in 87 instances of muscle spasm, significant improvement was achieved in over 90 per cent of the cases, including over 60 per cent in which recovery was marked to complete. Limitation of motion and shift of trunk also responded to some extent in most cases, although marked improvement or complete relief of symptoms was achieved less frequently, in from 40 to 55 per cent of the cases.

Side effects. As mentioned earlier, some patients became sleepy following the administration of meprobamate, particularly at the higher dose levels. This effect could usually be controlled by reduction of the dose or, in the few cases in which the higher dosage was indicated, the soporific effect could be adequately counteracted by the administration of small doses of amphetamine.

Two patients had pronounced sensitivity to meprobamate. One developed a fine erythema that subsided on withdrawal of the drug. This patient was found previously to have exhibited allergic reactions to other substances. The second patient developed an acute hypersensitivity reaction characterized by rash, urticaria, fever, and bronchial spasm. He recovered completely in 72 hours following antihistamine administration. This patient denied food allergies, but reported having developed urticaria and generalized erythema follow-

ing combined administration of sulfonamide and tetanus antitoxin 4 years earlier. Other side reactions were not observed. Since the analysis on our first 107 cases has been prepared, we have continued to administer this drug to many more patients and have noted 2 additional cases with similar adverse responses to the medication.

Comment

The need for an effective muscle-relaxing drug, both in general practice and in specialties dealing with spastic conditions, has long been felt. This need was only imperfectly met by mephenesin, which must be given intravenously or in large oral doses to achieve a transient therapeutic effect. When given orally, mephenesin proved of value in relatively few patients and there was always the possibility that unpleasant gastric disturbances would follow its use.

Meprobamate is, in all respects, greatly superior to mephenesin. It can be given orally, it is free from gastric side effects, and a dose is effective for a period of about 6 hours. The drug was used with consistently good results on over 100 unselected patients with varying diagnoses. Ninety per cent or more of the patients showed symptomatic improvement of pain and tenderness, muscle spasm, and limitation of motion.

Meprobamate is of inestimable value for use with aged patients with degenerative diseases, especially when cortisone is contraindicated. The drug does not interfere with the vital functions, cause sodium retention, or create autonomic imbalance.

A unique additional value of meprobamate is its tranquilizing effect. The drug calms patients made chronically irritable by pain, thereby both improving their mental state and increasing their physical comfort.

Recently we have been investigating the effect of combined meprobamate and minimal prednisolone therapy. The results to date have been encouraging, but the definitive answer will have to await further trial and study.

Summary and Conclusions

Meprobamate was administered to 107 patients with symptoms of muscle spasm, limitation of motion, pain and tenderness, and shift of trunk. It was found to be the best muscle relaxant available to date for use in these conditions. Significant relief was provided to nearly all patients, and particularly to those suffering from acute back strain and acute cervical myositis. Two patients with idiosyncrasies to the drug developed skin rashes. No other toxic reactions were observed. Meprobamate is fully effective on oral administration, is long-acting, and does not produce gastric disturbances or other undesirable results.

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THE EFFECT OF MEPROBAMATE ON CEREBRAL PALSY

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The syndrome known as "cerebral palsy" is an expression of disturbance in three areas of the physicopsychological structure of the individual. The symptoms are caused by damage to the *pyramidal* or to the *extrapyramidal* motor system, or to both. Manifestations of the disorder include (1) abnormalities of muscle control, (2) defective learning processes, and (3) aberrant psychosocial behavior patterns. Seizures and sensory defects (such as deafness, poor visual acuity, and difficulties in space perception) may complicate the picture.

In patients with pyramidal involvement the quality of muscle tonus is distinctly different from that in patients with extrapyramidal damage. The degree of tonus varies from individual to individual within each category and within the same patient at different periods of maturation or under varying conditions of stress, but the quality of tonus does not change.

Evidences of pyramidal disturbance may be distinguished from manifestations of extrapyramidal lesions by observation of the behavior of the muscles involved. In the pyramidal form the spastic muscles exhibit hyperactive deep tendon reflexes, clonus, and facilitated stretch reflex; they tend to form contractures that may be of stony consistency. In the pure athetoid, deep tendon reflexes are normal, or exaggerated if tension is increased. There is no true stretch reflex. Contractures rarely form; they are the result of malpositioning and may be corrected easily by stretching.

Elements of normal muscle behavior include: (1) function, which is dependent on co-ordination, strength, and intellectual control; (2) tone; and (3) the ability to relax involuntarily and reciprocally. This is demonstrated on the electromyographic tracing (FIGURE 1a), which shows asynchronous, irregular motor-unit discharges in the prime mover, with electrical silence due to reciprocal innervation in the antagonist. The top lead depicts the activity of the biceps; the bottom lead, the triceps. The action is the elbow flexion, demonstrating normal electrical activity in the prime mover and electrical silence in the antagonist.

As described by Rodriquez and Oester,[1] patients suffering from abnormality of the pyramidal tract exhibit continuous regular firing of motor units at a low, uniform amplitude (FIGURE 1b). Synchronicity of motor unit discharges is increased during contraction in spastic (pyramidal) disorders, with a reduction of total action-potential amplitudes. Spastic stretch reflexes are represented by tall spikes, with afterdischarges spreading to other levels or to the contralateral side of the same level. Activity is present in both the agonist and the antagonist.

In extrapyramidal lesions characterized by rigidity (FIGURE 1c), slight electrical activity is continuous, regardless of all efforts to relax. Total electrical output (summated voltages) is reduced during voluntary contraction, and abnormal synchronization of motor units is decreased.

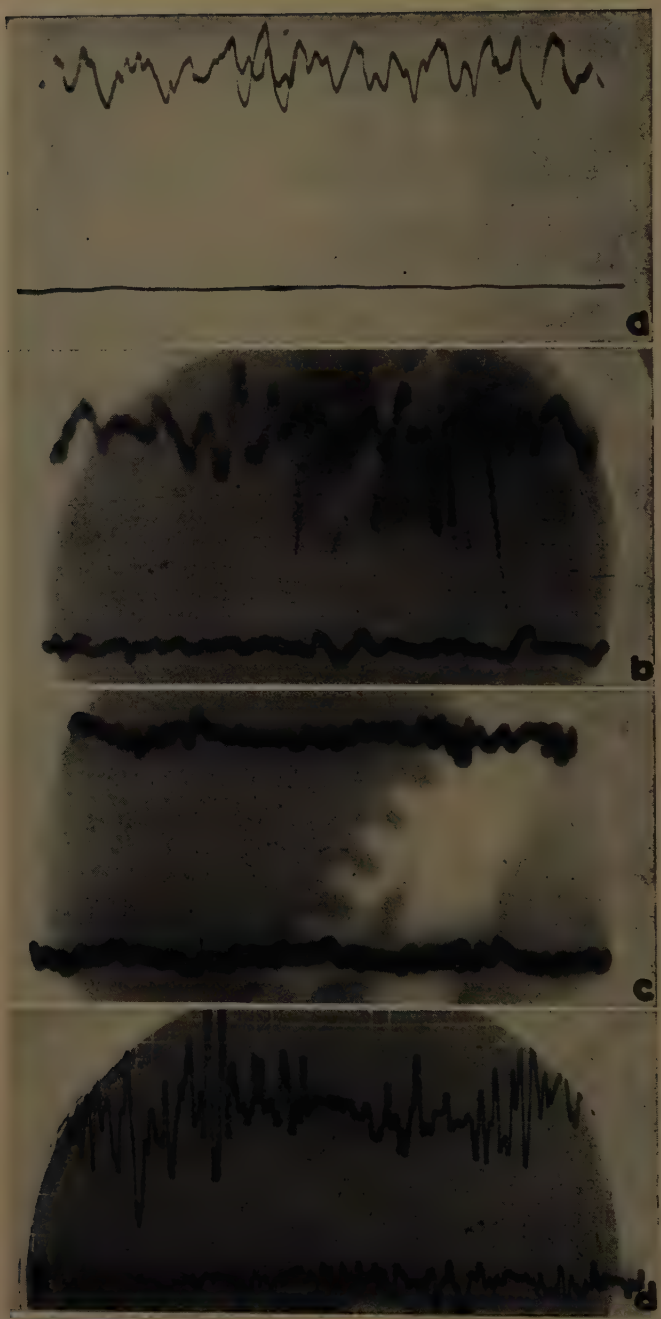

FIGURE 1. Records taken with surface electrodes during active elbow flexion (top record, biceps; bottom record triceps), showing (a) normal, with asynchronous activity in the biceps and electrical silence in the triceps; (b) spasticity, with synchronous discharges in the biceps and continued activity in the triceps; (c) rigidity, with synchronous low-amplitude activity in the biceps and triceps; and (d) athetosis, with asynchronous activity, with bursts of high-amplitude discharges and no relaxation of the antagonist.

In extrapyramidal lesions characterized by athetosis, it is impossible to achieve voluntary relaxation (FIGURE 1d). Unlike the situation in patients with rigidity, however, electrical silences definitely occur. The electromyographic tracing in individuals with extrapyramidal (athetoid) involvement exhibits irregular bursts of high-amplitude, high-frequency, asynchronous activity. In both forms electrical impulses may be recorded from the agonist and antagonist.

Much of the so-called progress that occurs with the passage of time in the child with cerebral palsy is the natural result of maturation. Supportive measures of various types are of value, however, in aiding the development of maximum ability to perform in the physical, psychological, and psychosocial spheres. Sensory handicaps may be minimized by the correction of visual defects and the use of hearing aids; seizures often may be controlled, completely or in part, by anticonvulsant drugs. Behavior difficulties may be ameliorated by appropriate counseling of the parents, and education within the intellectual limitations of the patient may be afforded by special teaching techniques. Contractures may be released, and muscles weakened by disuse may be strengthened by standard physiatric methods; braces and other special equipment may be employed to make use of movement patterns. Physical therapy, however, cannot alter the inherent tone of the muscle.

As emphasized by Magoun and Rhines,[2] "Any effective treatment of spasticity, and at present this field appears but in its infancy, must take into account the neurological features which are of importance in this condition. As we have tried to bring them out, these are (FIGURE 2): *one*, the spinal stretch-reflex; *two*, central inhibitory influences which reduce it; and *three*, central facilitatory influences which augment it—so that, expressed as an equation, *one* minus *two*, plus *three* equals spasticity." If the factors in the equation are quantitated, and if a drug can be found that will alter one or more of these factors, it should be possible to modify the result according to the purpose of the physician.

For many years one chemical substance has followed another in the endless search for a suitable compound to supplement standard physiatric measures in relaxing, strengthening, and stimulating increase of contractile range in muscles functioning abnormally as a result of brain damage. To be accepta-

Spinal stretch-reflex
minus
Central inhibitory influences which reduce it
plus
Central facilitatory influences which augment it
equals
Spasticity

FIGURE 2

ble, such an agent must, in a significant percentage of patients, (1) reduce muscle tonus to an extent demonstrable by objective methods; (2) exert prolonged action; and (3) avoid provoking or increasing the frequency of seizures, which depress the cortical areas (with clouding of consciousness), interfere with autonomic functions, or cause gastrointestinal irritation or other adverse effects. A few drugs have come into prominence, either because certain of their pharmacological properties appeared to offer some promise or because wide publicity attended a few reports of benefit.

Barbiturates, the only previously available drugs that could be used to quiet the emotionally tense patient, naturally were employed to relax muscle tension. Although phenobarbital relaxes contracted muscles, the concomitant sedation necessary to produce this effect is so profound as to render the patient nearly helpless. Moreover, in the brain-damaged child, the barbiturates frequently elicit excitement instead of a sedative response.

The results obtained with derivatives of belladonna have been inconsistent and unpredictable, particularly in postencephalitic rigidity. It has been impossible to determine the degree to which the changes seen in such patients subsequent to medication have been the result of convalescence and not the result of the action of drugs.

Prostigmine was popular for a brief period, largely because of enthusiastic articles in the lay press. Perlstein[3] demonstrated, however, that the changes attributed to this compound could be produced by the administration of placebos in conjunction with more vigorous physical therapy and the same attitude of optimism.

Curare aroused enthusiasm for a short time since, in many instances, the action of the substance on the motor end plates produces relaxation. However, the attendant danger of respiratory paralysis is too great to permit widespread adoption of this agent as a muscle relaxant.

Artane seems to be of value in a small percentage of athetoid patients with tension. Although successes obtained by means of it are few, nevertheless the compound should be included among the therapeutic possibilities for the management of cerebral palsy.

Mephenesin (FIGURE 3) represented a different approach to the problem of muscular tension. Intravenous injection of this compound produced a transitory period of relaxation. Administered by mouth, however, this drug was

Mephenesin

FIGURE 3

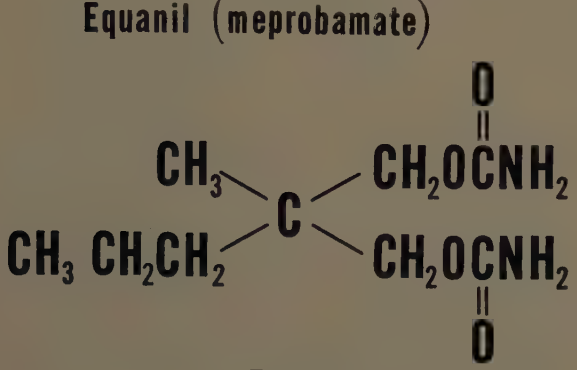

FIGURE 4

without effect. The untoward side actions—cortical depression and gastrointestinal irritation—have prohibited the use of mephenesin in large doses.

A chemically similar compound, meprobamate (FIGURE 4), derived from the 1,3-propanediols, has exhibited some promise for the relief of neuromuscular tension, and it appears to fulfill the requirements for a supplementary agent in the management of cerebral palsy. The compound has reduced muscle tone and has favored improvement in emotional control in a significant number of cerebral palsy patients[4] without producing untoward side effects, increasing hyperactivity, or lessening the attention span.

Plan of Study

This investigation involved a study of 53 patients with cerebral palsy, many of whom had already undergone preliminary observations.[4] Diagnoses were made according to the classical manifestations of spasticity, athetosis, rigidity, and tremor. No patients with ataxia or adults with paralysis from cerebrovascular accident were included in the series.

To simplify the problem of classification, the patients were grouped into two categories, depending on whether their cerebral lesions involved the pyramidal or extrapyramidal tract (TABLE 1). Twenty-three patients were suffering from pyramidal disturbances (group 1); 28 had suffered damage in the extrapyramidal area (group 2); and 2 fitted into both categories (that is, evidences of spasticity were present, but athetosis predominated); both were included in group 2.

Five patients were adults from 31 to 34 years of age. The others were children ranging in age from 3 months to 18 years. Seventy per cent of these were in the 3- to 10-year age group.

All had been under observation for several years or since birth. Thus, the physical attributes and the rate of development of all had been charted at regular intervals. In 94 per cent, the cerebral lesions had been present from birth. In the remainder, brain damage had followed accident, excision of cerebral tumor, or encephalitis.

Throughout the period of observation all patients were maintained on a

TABLE 1

	Patients
Group 1. Pyramidal involvement	23
Group 2.	
Extrapyramidal involvement	28
Evidence of spasticity, with athetosis predominating	2
	53

home program of active exercises; a few received physiatric treatment in addition to the home routines.

Medication. All patients received meprobamate orally. Those with pyramidal lesions received total daily dosages ranging from 300 mg. to 1.2 gm. per day. Those with extrapyramidal lesions received total daily dosages ranging from 150 mg. (in one infant) to 2.4 gm. per day. Most of the patients in both groups received 1.2 gm. daily.

Medication was continued for from 1 week to 6 months in the patients with pyramidal lesions. Of those with extrapyramidal involvement, slightly more than 50 per cent received the medication for from 4 to 8 months, and the remainder were maintained on the compound for from 1 to 3 months. All who showed appreciable benefit are continuing to receive the medication.

It was necessary to discontinue the drug for 2 patients in group 2—in two days for one, because of vomiting, and in 2 weeks for the other, because of a prolonged convulsion, although favorable effects were obtained on tension, emotional control, and increase of function.

Method of evaluation. As previously reported,[4] direct observations were made in each instance by the same physician and therapist who had treated

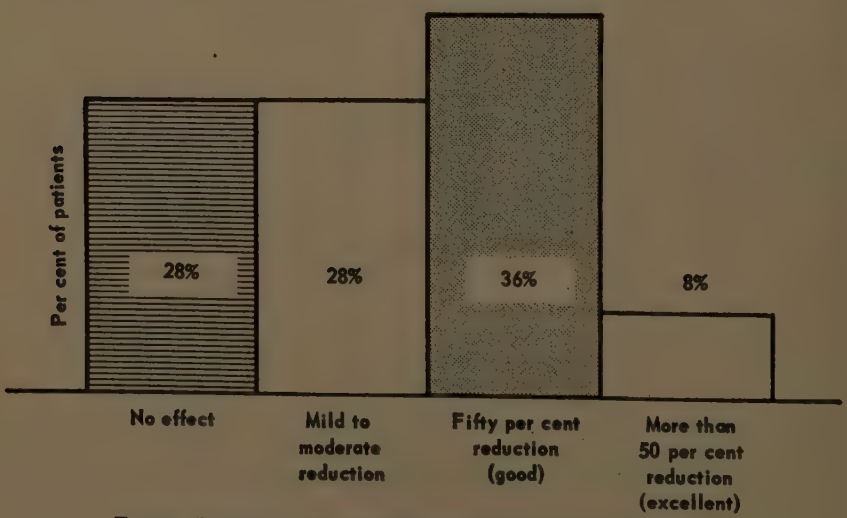

FIGURE 5. Group 1: pyramidal lesions (reduction in spasticity).

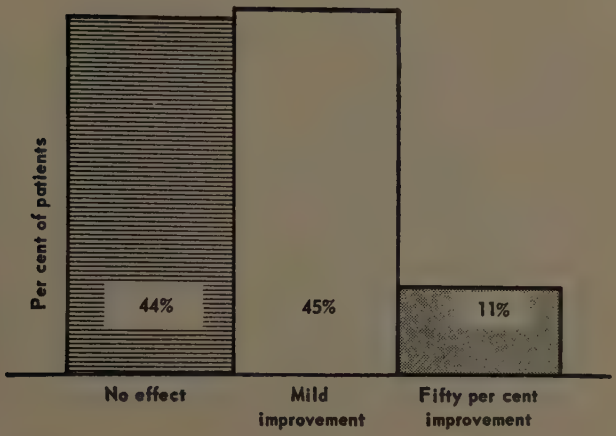

FIGURE 6. Group 1: pyramidal lesions (greater ease in stretching).

the patient initially. In evaluating the patient, the degree of involvement was graded as 4 plus (severe), 3 plus (moderate), 2 plus (mild), and 1 plus (slight), according to the intensity of the stretch reflex, the degree of muscle tone, and the tendency to form contractures. Response was graded according to the extent to which symptoms had lessened. Objective criteria, such as the development of new purposeful movements, increase in head control or grasp, and greater ease of bracing, were used.

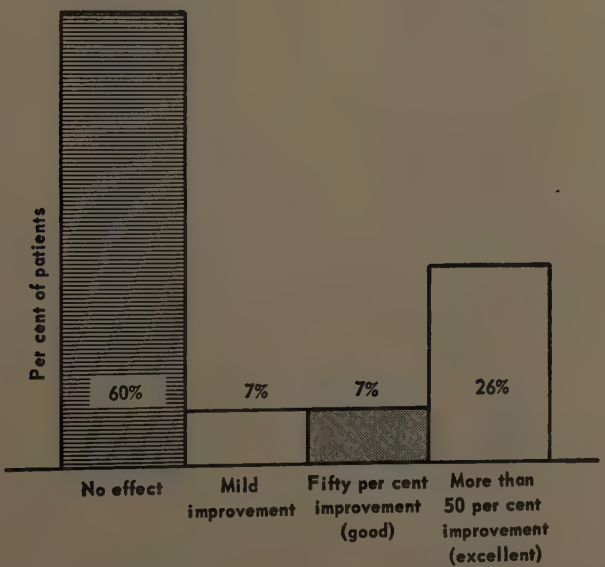

FIGURE 7. Group 1: pyramidal lesions (improvement in emotional control—less screaming, crying, and irritability).

In those instances in which appreciable improvement occurred in response to medication, the *feel* of the muscle to the examiner's fingers changed from resistance of a sharp, well-delineated type to a more fluid, less well-defined, less constricted resistance as the segment was moved. Significantly less force was required in the patients with tension.[2]

In spastic patients, the stretch reflex remained but was less forceful and, in patients showing a response to the drug, stretching could be performed more easily. There appeared to be no effect on the consistency of the stony contracture itself; the greater ease in stretching appeared to be confined to the muscle belly.

Observations at physical examination were confirmed by electromyographic studies. All tracings were taken with surface electrodes placed on the biceps and triceps. Calibration was 200 μv., with a sweep of 30 per sec. The upper tracing recorded the activity of the biceps, and the lower tracing represented the action of the triceps.

Results

In group 1 (patients with pyramidal lesions), spasticity was reduced to some extent in 72 per cent (FIGURE 5), the mean improvement being mild to moderate. Stretching (FIGURE 6) became easier in 56 per cent. Emotional con-

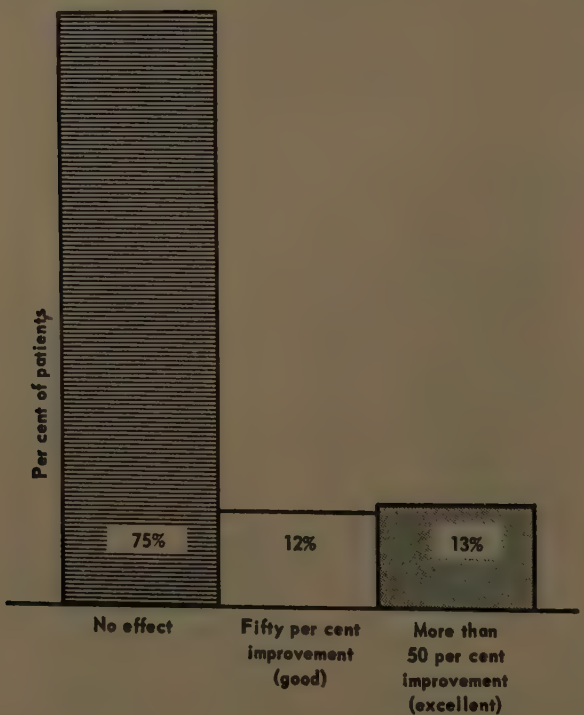

FIGURE 8. Group 1: control of hyperactivity.

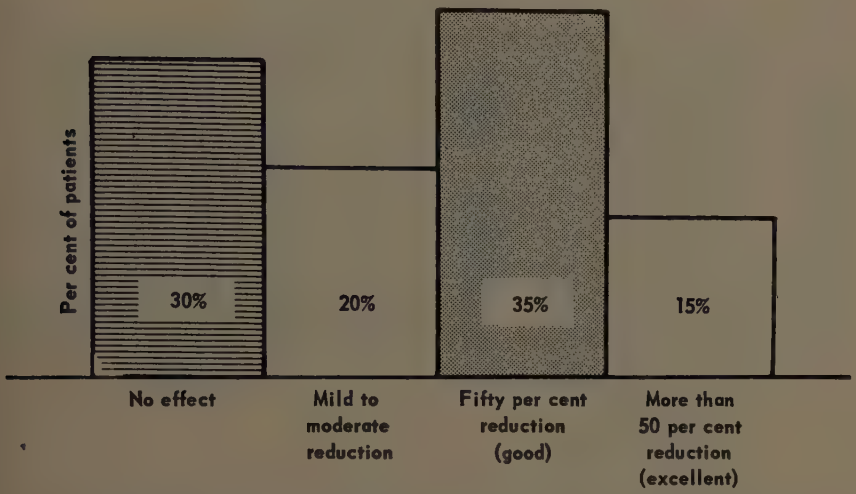

FIGURE 9. Group 2: extrapyramidal lesions (reduction in tension).

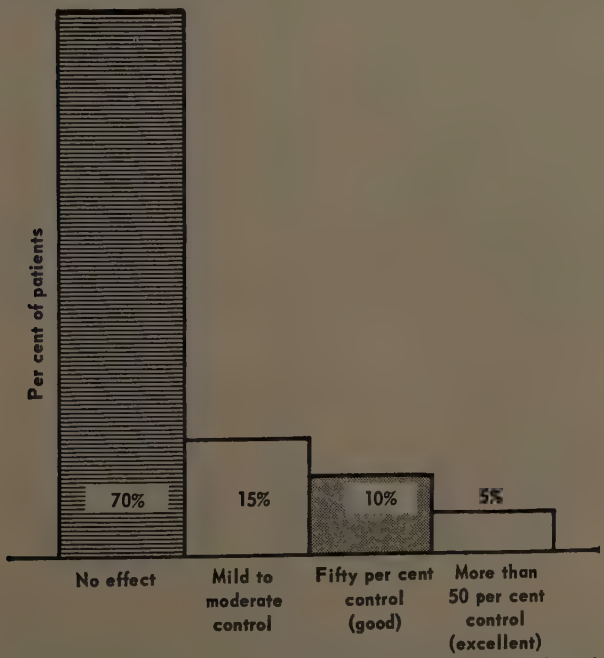

FIGURE 10. Group 2: extrapyramidal lesions (control of athetosis).

trol (FIGURE 7) improved in 40 per cent; that is, there was less screaming, crying, and irritability. Hyperactivity (FIGURE 8) was controlled to some extent in 25 per cent.

In group 2 (patients with extrapyramidal lesions), 70 per cent (FIGURE 9)

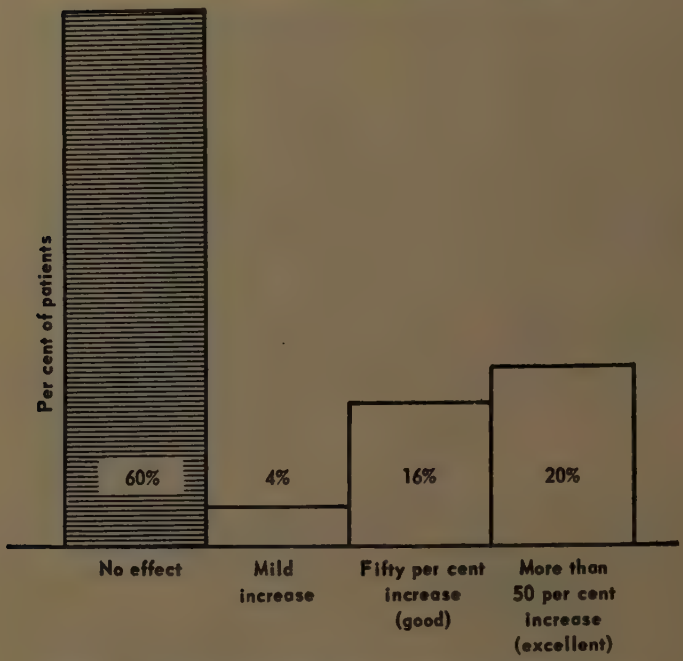

FIGURE 11. Group 2: extrapyramidal lesions (increase in function).

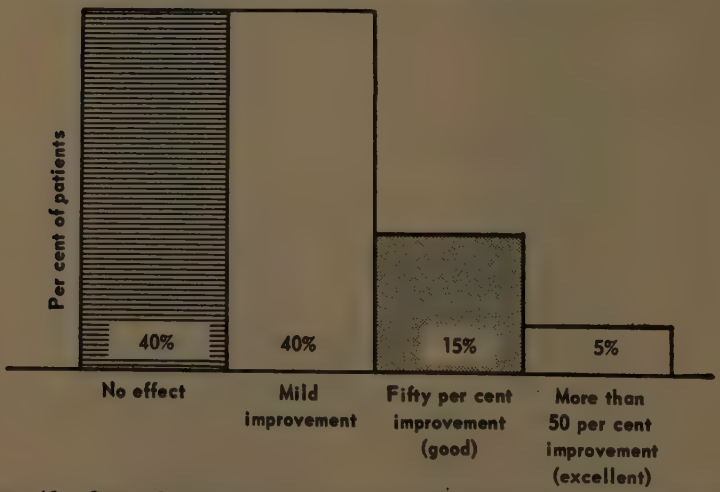

FIGURE 12. Group 2: extrapyramidal lesions (improvement in emotional control—less screaming, crying, and irritability).

showed some reduction in tension, with the mean improvement being good (50 per cent) or better. Thirty per cent showed some improvement in the control of athetosis (FIGURE 10). Forty per cent showed some increase in function (FIGURE 11). Sixty per cent (FIGURE 12) showed some improvement in emotional control (less screaming, crying, and irritability).

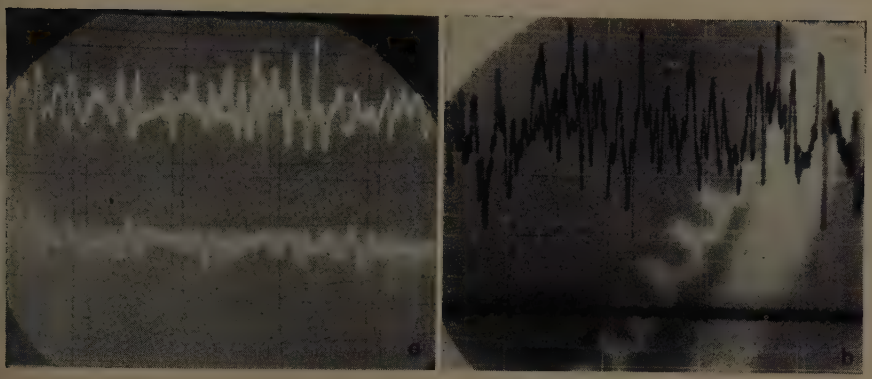

FIGURE 13. Records of the same case of athetosis (a) without medication and (b) with medication, showing, in the latter, a reduction of activity in the antagonist. In each figure the the top record depicts the activity of the biceps; the bottom record, the triceps.

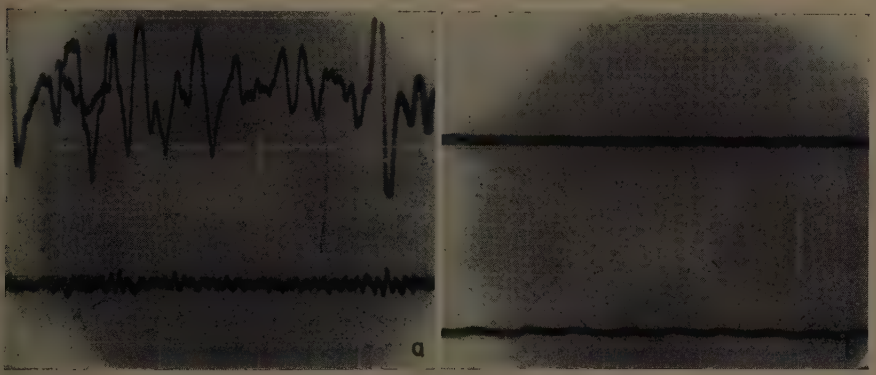

FIGURE 14. Records of the same case of athetosis with very severe tension, after having been on meprobamate for one year, during which there was excellent clinical improvement. FIGURE 14a shows active elbow flexion (note the slight activity in the triceps); FIGURE 14b, voluntary relaxation on command.

To illustrate the changes that occurred, the electromyographic tracings shown in FIGURES 13 to 17 were taken, first during periods without medication and, later, after medication had been instituted.

Discussion

The results obtained in this series must not be construed as indicating that meprobamate is a "cure-all" or "miracle drug" for the management of cerebral palsy. The compound does favorably affect muscle tone, and it exerts a tranquilizing action in certain cases. Thus, in the patients who respond to medication, especially those with extrapyramidal lesions, there is definite ability to perform purposeful movements or to achieve better head control, increase in grasp, or greater ease in bracing, as determined according to objective criteria. In patients with pyramidal damage, however, there is a tendency toward emotional instability that may reach severe proportions.

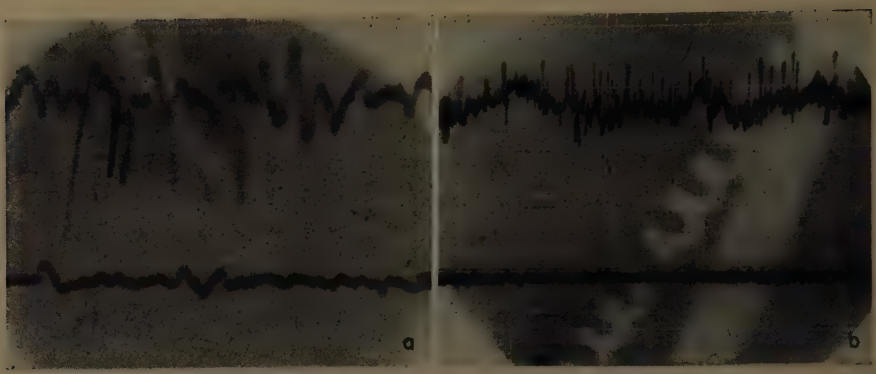

FIGURE 15. Records of the same case of spasticity (a) without medication, showing high amplitude and synchronous activity without inhibition of the antagonist, and (b) with medication, showing the nearly complete inhibition of the antagonist.

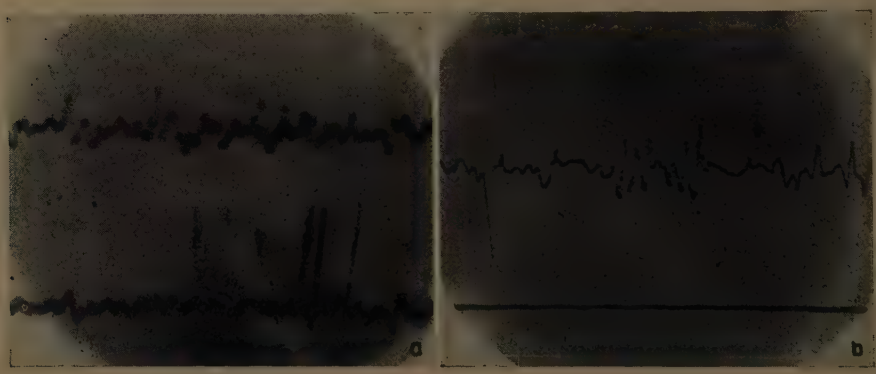

FIGURE 16. Records of the same case of rigidity (a) without medication, showing low amplitude and synchronous activity in the agonist and antagonist, and (b) with medication, showing how the release of tension brought about bursts of involuntary motion and the complete inhibition of the antagonist.

Summary

Fifty-three cerebral palsy patients received medication with meprobamate. Twenty-three were suffering from pyramidal damage, 26 had extrapyramidal lesions, and 2 fitted into both categories.

Direct physical examinations were supplemented by electromyographic studies made during periods without medication and after treatment with the drug had been instituted.

It was apparent that meprobamate effected a change in some part of the central nervous system in a certain percentage of patients. This change was manifested clinically by improvement in function, as expressed by the development of new purposeful movements, increase in head control or grasp, or greater ease in bracing. In most cases, however, increase in function was moderate.

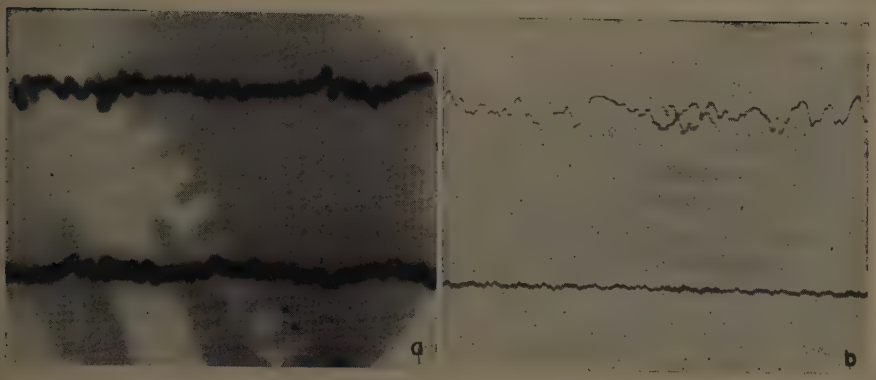

FIGURE 17. Records of the same case of rigidity (a) without medication, showing continuous synchronous activity in the agonist and antagonist, and (b) with medication, showing asynchronous activity in the prime mover, with reciprocal inhibition of the antagonist.

When a measurable alteration was determined in the feel, to the examiner's fingers, of the muscle during contraction (best described as ductility), the electromyographic tracing also demonstrated a change somewhere in the central nervous system which augmented facilitation and reciprocal and voluntary inhibition.

Case Histories

Case 6, group 2. This child was first seen in 1954, at 6 years of age. Tension was severe; the heels were literally touching the occiput. There was no speech and, of course, no purposeful movement. The girl's weight had remained constant at 20 lb. for 3 years. Neurosurgical procedures to enable maintenance of the child in a crib without self-injury had been under consideration. Surgery was deferred for an additional year; on re-examination there was some decrease in tension. The child could utter a few simple words and had acquired some grasping motion, but still could not be maintained in a chair.

At this point medication with meprobamate was begun with a dosage of 200 mg. 3 times a day. For the first 2 months there was rapid change; first there was an initiation of jabbering, followed by the ability to pronounce 3 to 4 word phrases. At the end of the first 2 months the child began to bring her hand to her face and to maintain her head in the erect position. Improvement continued steadily, but at a somewhat slower rate. One year after the initiation of meprobamate therapy the child was able to sit in a chair without restraint, could bring her hand to her mouth, presented no problem in feeding, was able to chew gum, spoke 5-word sentences with fair articulation, acquired a reciprocal walking pattern when held erect, and had gained 12 lb. (FIGURE 14b)

Case 8, group 1. A 32-year-old female with a diagnosis of spastic quadriplegia, with severe spasticity and severe scoliosis producing radicular pain. Meprobamate was administered in a dosage of 400 mg. 3 times a day for 3 months. Spasticity decreased to a moderate degree, and ambulation became

somewhat easier and faster. The radicular pain diminished. Emotional instability was intensified, however, with an increase in depression and frequent crying. Despite the favorable effect on the musculature, it was necessary to discontinue the compound.

Case 6, group 1. A 4-year-old boy with a diagnosis of hypotonic spastic quadriplegia and severe mental and physical retardation. The child's excessive crying and irritability created many family problems. For tranquilization, meprobamate was administered in a dosage of 800 mg. daily. Instead of responding as expected, the child began screaming almost constantly, and the drug was discontinued. There was no change in muscle status.

Case 14, group 2. A 10-year-old girl with a diagnosis of rigidity with severe tension. This patient had been known to the examiner since the age of 4 years and had been constantly on a full home-exercise program, with additional treatment by a qualified physical therapist. Muscle tension was severe (FIGURE 17a) and there had been no change in function in any respect in the 6 years she had been under observation. With the exception of a difficult reciprocal walking pattern and a momentary grasp, voluntary activity was impossible.

In May 1956, meprobamate was begun in a dosage of 400 mg. 3 times a day. After 4 months the child was able to propel and guide her tricycle unassisted and to use a walker, also without assistance. The time span of her capacity to grasp had doubled, and she had begun reaching for objects. She was able to sleep all night without being awakened, whereas formerly, because of forceful hip and knee flexion motions, this had been impossible. She was participating in a rhythm band and, although her articulation was poor, had begun to pronounce single words. The therapist reported that her ranges of motion had increased and that her contractures were more easily stretched. According to the therapist, her distractability had not been affected.

On September 1, 1956, the mother was requested to test the effect of the drug by omitting the dose. Within 2 days the child was unable to ride her tricycle or use her walker, and she awoke several times during the night with her legs in spasm. Her speech became more labored and finally stopped. The therapist reported that, without the drug, the child, although seemingly more alert, was unable to follow commands as she had done previously under medication. The child's ranges of motion decreased, and contractures became more rigid. The drug was then reinstituted, and the activities that previously had been possible were resumed. Within a few days the tracings were repeated under medication (FIGURE 17b).

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THE EFFECT OF MEPROBAMATE ON THE BASAL GANGLIA*

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If one attempts to analyze the effect of a tranquilizing agent such as meprobamate, studies of scalp electroencephalograms (EEGs) are somewhat disappointing, since they show relatively few changes. Electrographic recordings obtained from the subcortex may, however, be of interest. We have recently had the opportunity to study the effect of tranquilizing drugs on the subcortices of patients who had extrapyramidal and/or convulsive disorders. Also, in order to study the effects of the drug upon the normal central nervous system, short- and long-term experiments have been performed in cats. Some of these studies were obtained without additional anesthesia; in others, anesthesia with Dial (0.55 c.c./kg.) was employed. The techniques for these stereotaxic procedures and for the insertion of subcortical electrodes have been described elsewhere.[1]

In the experiments with animals, the finding of Hendley *et al.*,[2] that meprobamate acted chiefly upon the diencephalon, was confirmed. In our experiments, also, this effect was marked in the dorsal thalamus. Initially, slow waves appeared in this area. The depression of activity occurred with relatively small doses (20 mg./kg.) in various nuclei; for example, in the dorsomedial nucleus (FIGURE 1), the centrum medianum, and the nucleus ventralis posterior (FIGURE 2). In the hypothalamus, however, slow waves that were present before injection of the drug were replaced by fast activity (FIGURE 3A), or there was an increase of the amplitude of pre-existing fast waves (FIGURE 3B). This is in contrast to other tranquilizing agents such as reserpine and chlorpromazine, for which a reduction of hypothalamic activity has been assumed.

The effect of meprobamate, however, is not restricted to the diencephalon. It also alters the electrical activity of subcortical ganglia within the prosencephalon. In FIGURE 4 a definite slowing of the discharges from the amygdala following the administration of meprobamate is demonstrable. Similarly, slow waves also appeared in the electrogram of the caudate nucleus. In one experiment, however, in which chlorpromazine had been administered intravenously, spike discharges appeared in the caudate nucleus following the intravenous administration of meprobamate. In another experiment, single spike discharges appeared in the putamen of a cat under anesthesia with Dial following an intracardiac injection of meprobamate. In analyzing the effect upon the basal ganglia, the possibility should be considered that the depressive action of meprobamate upon the striatum may be a secondary effect due to diminution of the afferent impulses from the thalamus. Previous experiments by Spiegel *et al.*[3] have shown that the basal ganglia receive numerous afferent impulses from the thalamus.

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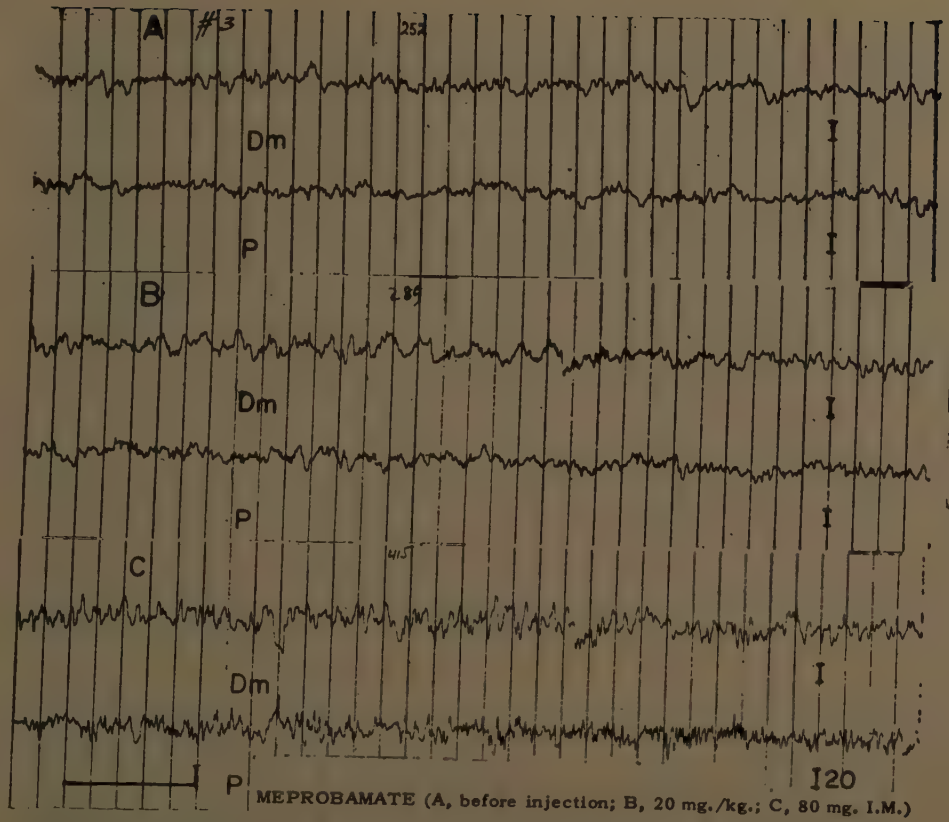

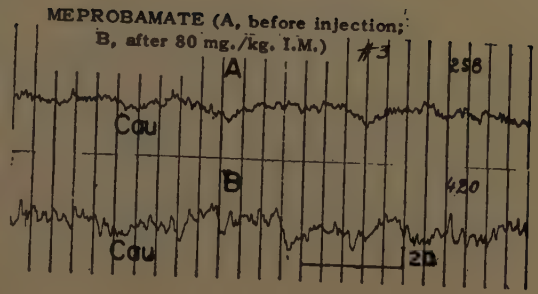

FIGURE 1. *Cat.* Effect of meprobamate upon the dorsomedial nucleus (Dm), pallidum (P), and the caudate nucleus (Cau). The time in all figures is 1 sec. All standardizations are in microvolts.

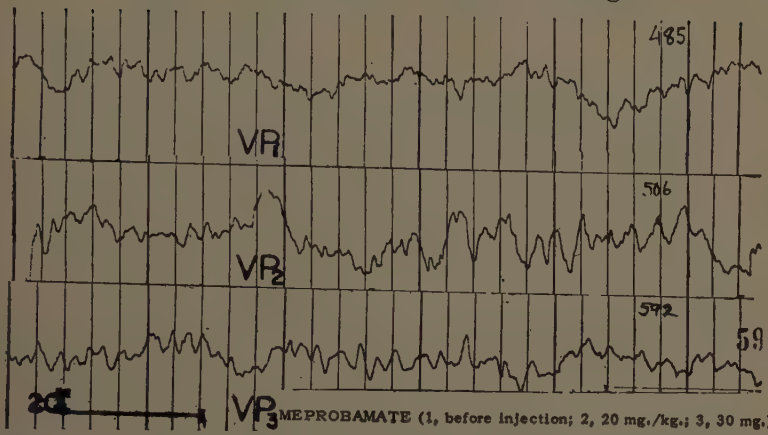

FIGURE 2. *Cat.* Effect of meprobamate upon the nucleus ventralis posterior of the thalamus.

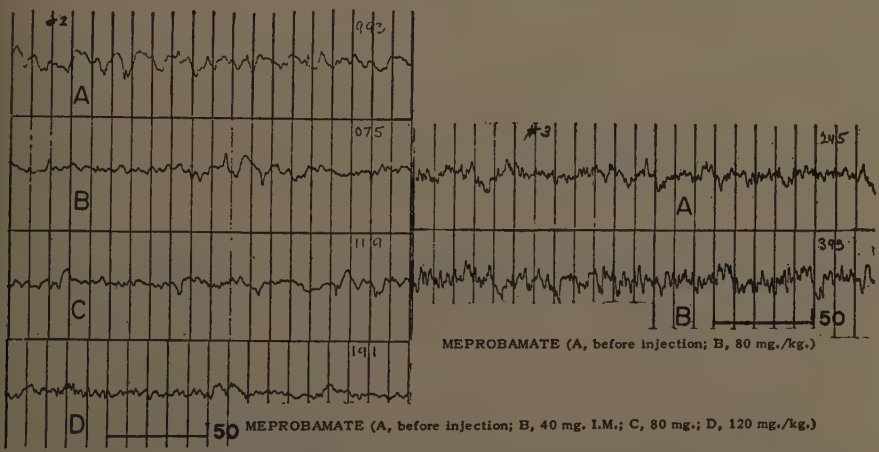

FIGURE 3. *Cat.* Effect of meprobamate upon the hypothalamus. In the experiment reproduced in the left part of the figure, the hypothalamus showed slow waves before and fast activity after injection. In the experiment illustrated in the right part of the figure, the fast activity existing before injection was increased in amplitude after application of the drug.

There are findings suggesting a direct action of meprobamate upon the basal ganglia, however. It could be repeatedly observed that the striatum and the pallidum often appeared to react somewhat independently of each other. For example, a slowing of the waves in the caudate nucleus may be associated with an increase of the fast activity in the pallidum (FIGURE 1). Conversely, the appearance of spike discharges in the caudate nucleus may be accompanied by a decrease of the pallidal activity (FIGURE 5B), or slowing in the caudate may appear without definite changes in the pallidal discharges (FIGURE 6). In view of the fact that efferent impulses from the striatum end in the pallidum, one would, of course, expect that a change in the state of excitation of the striatum would induce similar changes or, in case of inhibition, that there would be opposite changes in the pallidum. The fact that a dissociation in the effect upon the pallidum and upon the striatum may be ob-

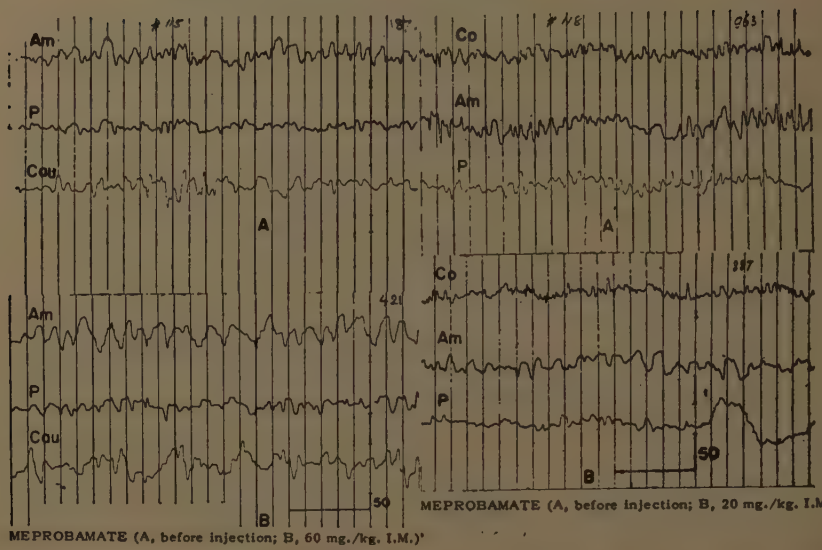

FIGURE 4. *Cats.* Effect of meprobamate upon the amygdala (Am), the caudate nucleus (Cau), the pallidum (P), and the cortex (Co). In both animals there was a definite slowing in the amygdala and a slight slowing in the caudate nucleus.

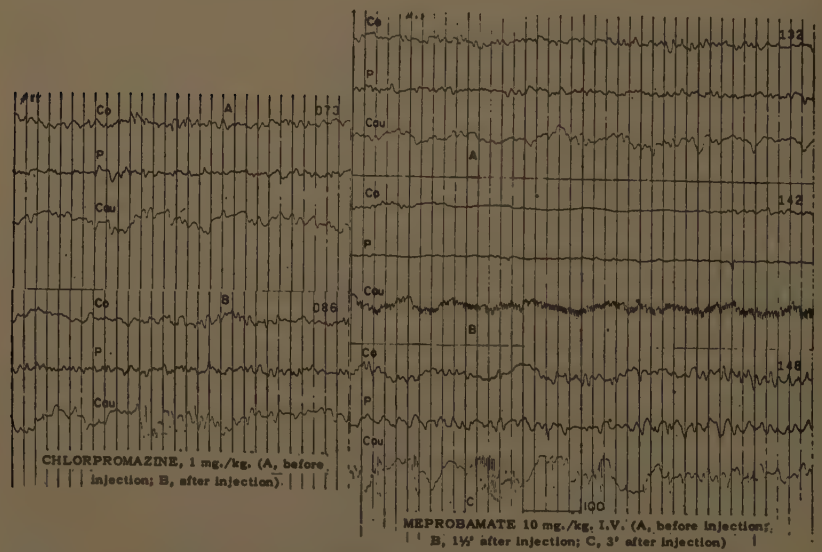

FIGURE 5. *Cat.* Effect of the intravenous injection of chlorpromazine, producing spike discharges in the caudate nucleus (Cau). Subsequent injection of meprobamate increased the spike discharges in the caudate (Cau), but depressed the pallidal activity (P shows flattening in B, slow waves in C).

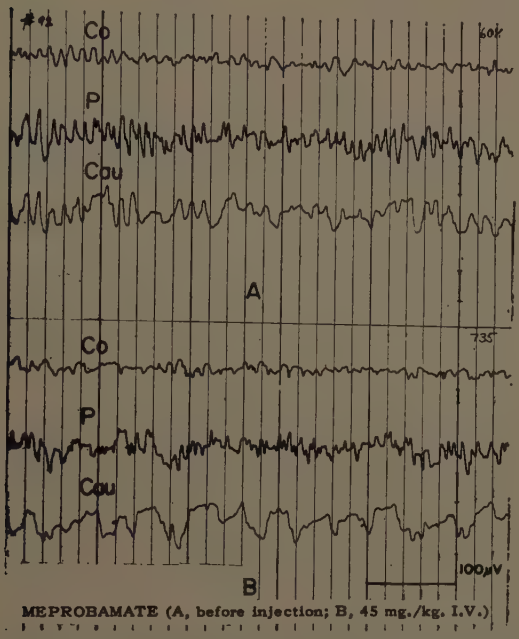

FIGURE 6. *Cat.* Effect of meprobamate upon the caudate (Cau), the cortex (Co), and the pallidum (P). Note the slowing in the caudate despite the fast activity in the pallidum.

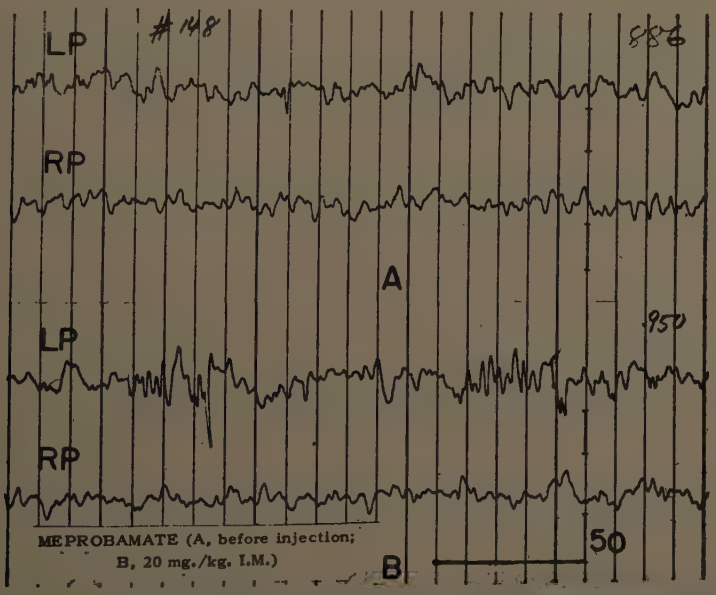

FIGURE 7. *Cat.* Effect of meprobamate upon the pallida 5 weeks following lesion of the left caudate. Note the increased reaction in the left pallidum (LP) as compared with the right pallidum (RP).

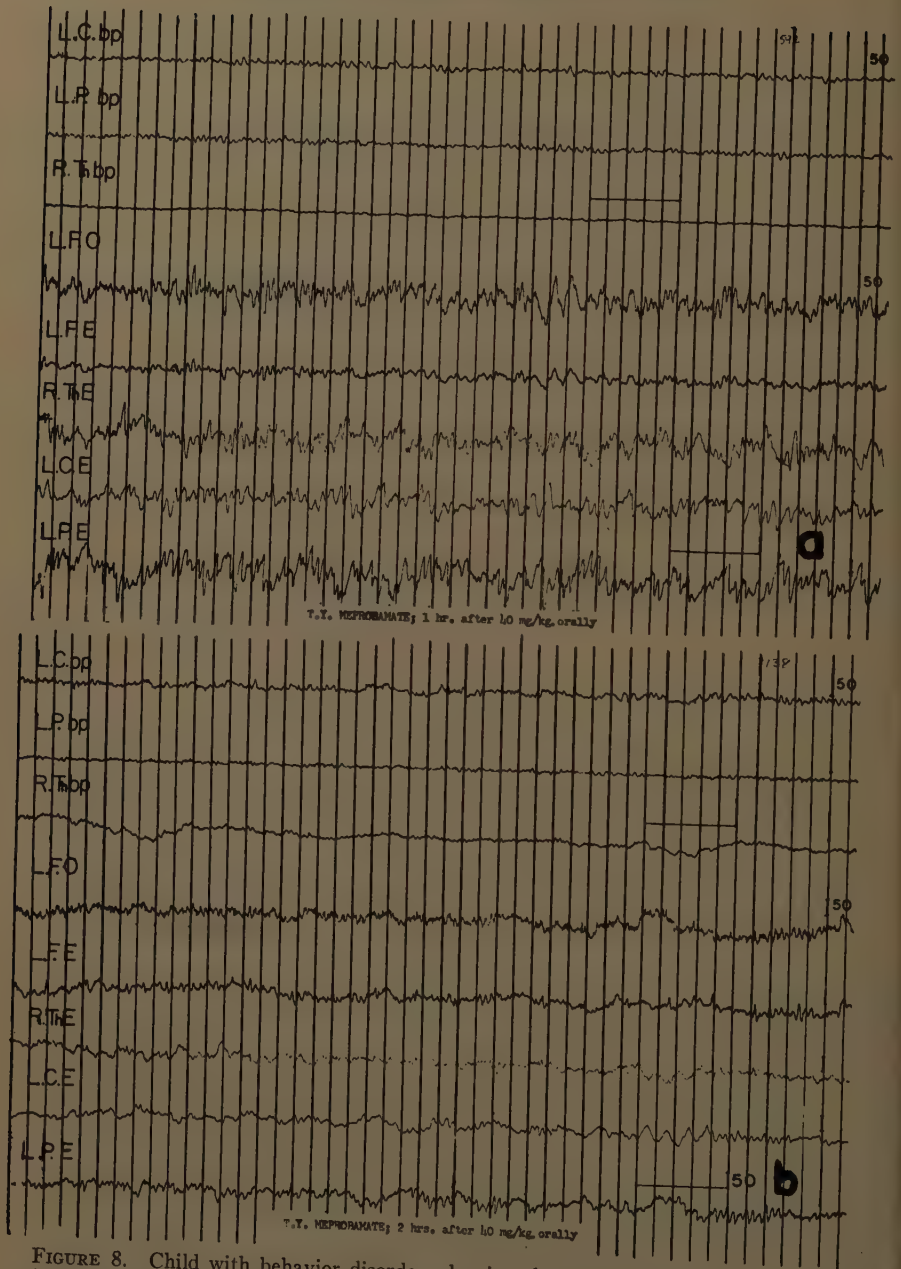

FIGURE 8. Child with behavior disorder, showing the effect of meprobamate upon the scalp EEG and upon the caudate (C), the pallidum (P), and the thalamus (Th) one hour and two hours after the oral application of meprobamate (40 mg./kg.). In all the graphs, *L* signifies left; *R*, right; *bp*, bipolar; *F*, frontal; *O*, occipital; and *E*, ear.

served seems to suggest that a direct action of meprobamate upon the pallidum can antagonize the effect of striofugal impulses to this ganglion and supersede their action.

The effect upon subcortical ganglia seems to depend to a large extent on the mode of application of the drug. For instance, following intramuscular injection of 80 mg./kg. (without additional anesthesia), an increase of the fast activity of the pallidum was observed whereas, after intravenous administration of 40 mg./kg., the record became first flat, and then slow waves appeared. It may also be noteworthy that spike discharges in the striatum were noted on intravenous or intracardiac application only, so that the drug reached these ganglia rather rapidly.

It seemed of special interest to ascertain how the basal ganglia reacted to the drug when their state of excitation or their excitability was changed by central lesions. In this respect, the effect of chronic lesions in the caudate nucleus upon the susceptibility of the pallidum to toxins was studied. FIGURE 7 shows such an experiment. In this case an electrolytic lesion was produced in the left caudate nucleus and, following the injection of meprobamate, fast high waves appeared in the pallidum on the side of this lesion only. Thus, the effect of the toxin upon the pallidum was more pronounced on the side of the striatal lesions than on the opposite side where the caudate nucleus was intact.

A possible explanation is that, following lesions of the caudate nucleus, the pallidum is deprived of one of its main sources of afferent impulses, so that a state of partial isolation of this ganglion results. The supersensitivity of completely or partially denervated structures studied in recent years, particularly by Cannon,[4] also seems to apply to the ganglia of the extrapyramidal system and to result in an increased effect of toxins upon the pallidum.

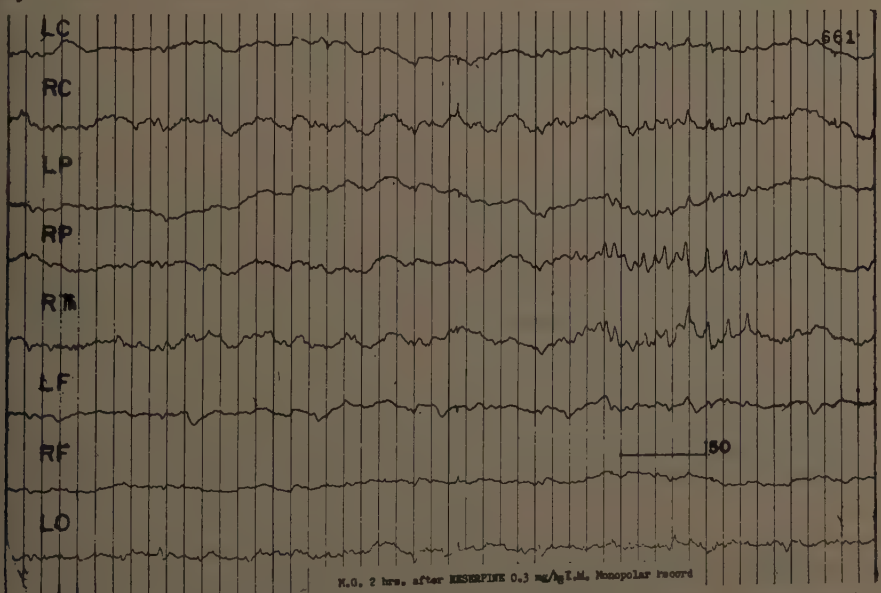

FIGURE 9. Torsion dystonia with concavity of the trunk to the left side. Under reserpine sedation, sharp waves appear in the right pallidum and thalamus.

Following this introductory survey of experimental studies from our laboratory, we should like to review our studies in children. The difference in action of the drug upon various parts of the subcortex is more clearly demonstrable in a state of slight drowsiness produced by meprobamate than in deep sleep. This may be illustrated by records from a patient with a severe behavior disorder (FIGURE 8a) that were obtained when the child was in a state of drowsiness. Under these conditions, monopolar records showed that the effect upon the thalamus was more pronounced than that upon the pallidum, and the least effect was noted in the caudate nucleus. Such differences in the reactions of these ganglia ceased to be demonstrable as the depth of sleep increased (FIGURE 8b).

The slight sedation induced by meprobamate also facilitates the electroencephalographic demonstration of pathological changes in the basal ganglia. For instance, in a child with athetosis (reported previously[5]) a marked slowing in the caudate nucleus could be demonstrated; this far exceeded the effect of similar doses of the drug in animals or in other patients. In children with extrapyramidal disorders who are under slight sedation, as produced by meprobamate or reserpine (FIGURES 9 and 10), asymmetries in the functional state of the basal ganglia may also become manifest on depth electroencephalography. It must be emphasized that an accentuation of an electroencephalographically demonstrable asymmetry is not necessarily associated with an increase of the clinical signs of motor dysfunction. The cause for this discrepancy remains to be studied. Tentatively, it may be hypothesized that the depres-

FIGURE 10. Graphs of the same patient as in FIGURE 9 under the influence of meprobamate. The slow waves are noted in the right pallidum (RP) and the right thalamus (R Th). Fast activity predominates in the right fronto-occipital (RFO), the left fronto-occipital (LFO), and the left frontal monopolar (LFE) scalp records. Some slowing is observed in the LFE record.

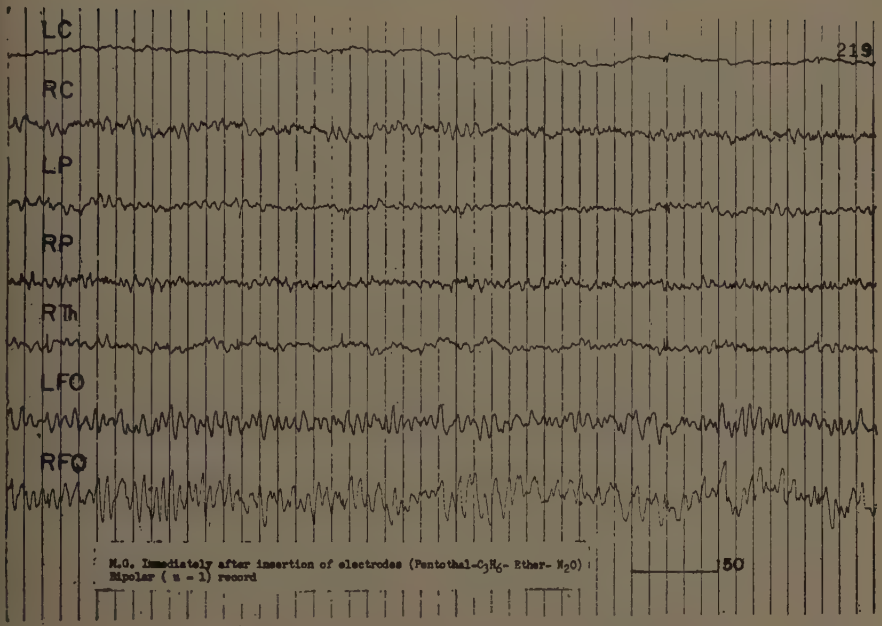

FIGURE 11. Graphs of the same patient as in FIGURES 9 and 10 immediately after barbiturate anesthesia. No definite asymmetry can be found.

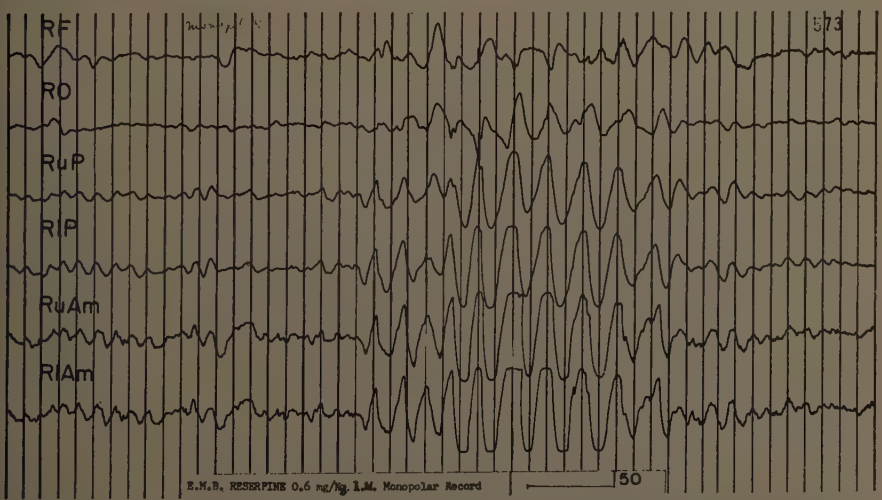

FIGURE 12. Child with convulsive disorder—monopolar record under reserpine sedation. High slow waves appear in the right amygdala (Am) and the right pallidum, preceding and more marked than in the scalp electrodes from the right frontal and right occipital leads. The upper electrode is signified by *u* and the lower by *l*.

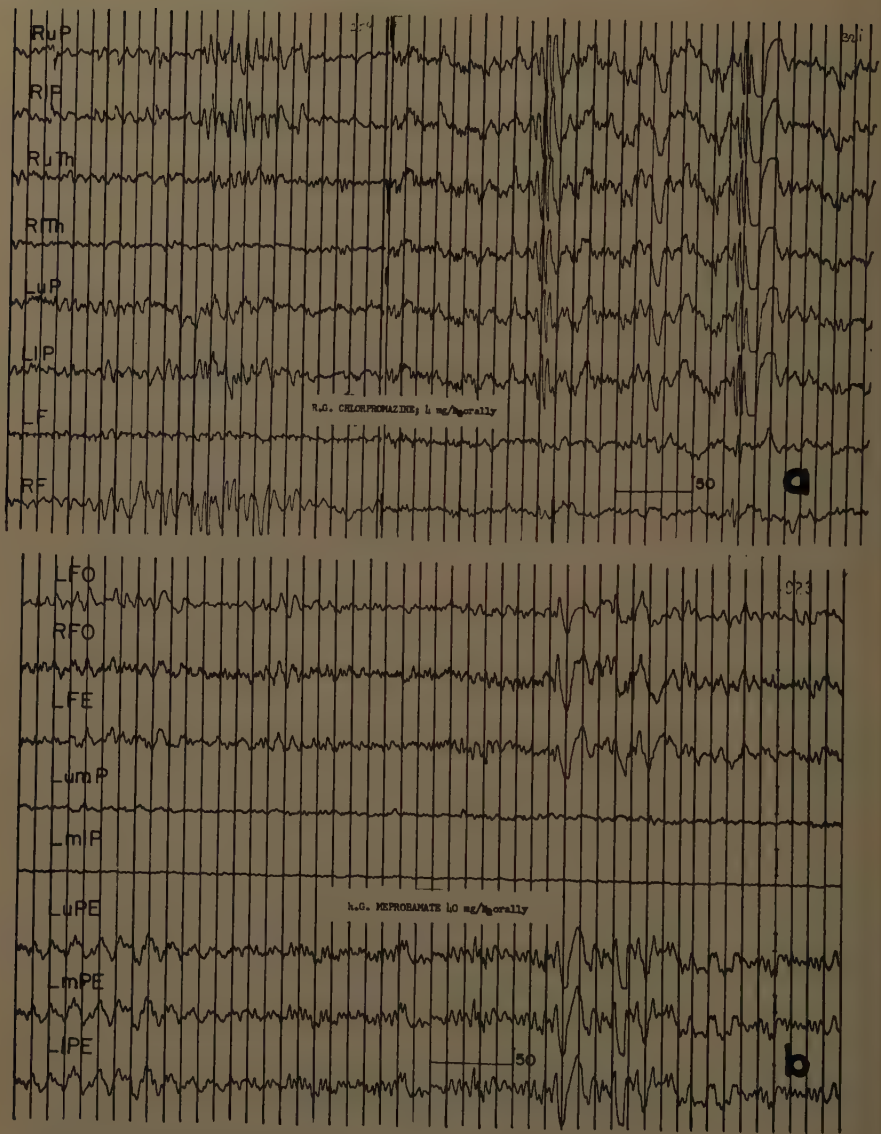

FIGURE 13. Child with convulsive disorder. FIGURE 13a shows that the spike discharges appearing under the effect of chlorpromazine are more marked in the pallidum (P) and the thalamus (Th) than in the frontal scalp (F). Between the two records there was a time interval of about one hour. FIGURE 13b shows the graph of the same patient under meprobamate. The seizure discharges are seen in the scalp leads (fronto-occipital, FO). Apparently simultaneous pallidal discharges are found in the monopolar leads from the upper (*u*) as well as from the middle (*m*) and the lower (*l*) pallidal electrodes, but they are not recognizable in the bipolar records.

sive action of meprobamate upon multisynaptic systems, demonstrable (according to Hendley *et al.*[2]) as far down as the spinal cord, may prevent this accentuation of asymmetry in the functional state of the pallida from becoming manifest in the respective effector apparatus. Again it should be noted that,

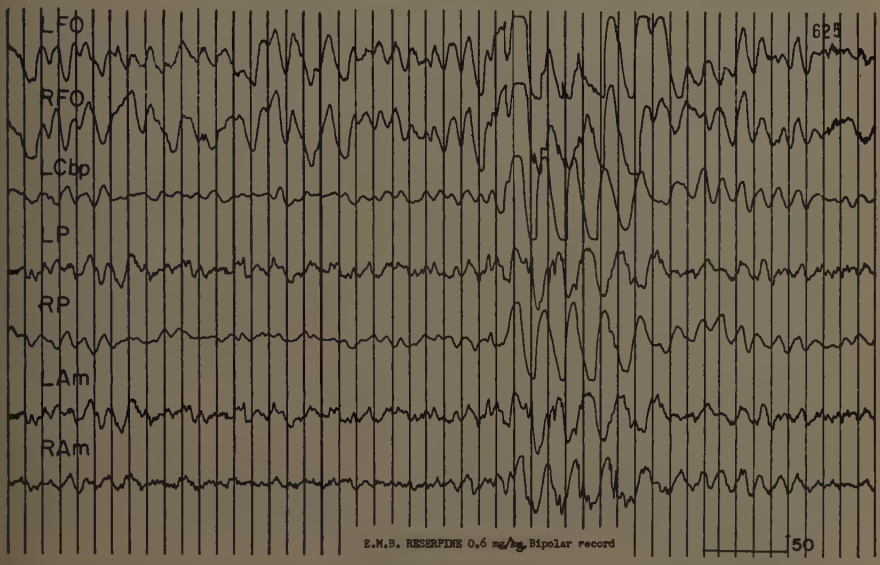

FIGURE 14. Child with convulsive disorder under reserpine sedation. The seizure discharges in the fronto-occipital records (FO) precede those in the caudate (C), the pallidum (P), and the amygdala (Am). All records on the subcortical ganglia are bipolar (bp).

FIGURE 15. Child with convulsive disorder under promazine sedation. Discharges from the subcortical ganglia (upper and lower pallidum electrodes, upper and lower amygdala electrodes) precede those in the frontal and occipital leads.

in the state of slight sedation, as produced by meprobamate or by reserpine, such anomalies become more distinct than if a deeper depression is produced by general anesthesia (FIGURE 11).

The state of slight sedation produced by meprobamate or by reserpine is also favorable for the demonstration of subcortical seizure discharges in some cases of convulsive disorders (FIGURE 12). The appearance of such seizure discharges in subcortical areas need not be associated with a clinical seizure, just as abnormal discharges may be found in the scalp EEG of a child who does not have a seizure at the time of his recording. Seizure discharges have been recorded from the basal ganglia (FIGURE 12) when no or only very slight abnormalities were apparent in the scalp EEG. There are, however, also instances in which such abnormal discharges appear in the scalp EEG, as well as in the electropallidogram and/or the electroamygdalogram. These discharges may appear simultaneously in all areas under study (FIGURE 13), as far as can be ascertained by means of an ink electrograph. One may, however, also observe seizure discharges starting in the cortex (in the scalp EEG) and propagated to the subcortex (FIGURE 14); conversely, subcortical discharges may precede those recorded from the scalp (FIGURE 15).

Summary

(1) Experimental studies in cats showed that the action of meprobamate is not limited to the diencephalon, but extends to forebrain ganglia (amygdala, caudate nucleus, pallidum) in varying degrees.

(2) A dissociation in the effect on the pallidum and on the caudate nucleus may be observed, indicating differences in the susceptibility of these ganglia to meprobamate.

(3) Lesions of the caudate nucleus may induce a supersensitivity of the pallidum to the action of meprobamate.

(4) In children, a difference in the action of meprobamate upon various subcortical ganglia could also be noticed (for example, more pronounced effect upon the thalamus than upon the pallidum, particularly with mild sedation).

(5) Mild sedation induced by meprobamate or by reserpine may reveal asymmetries in the functional state of the basal ganglia in extrapyramidal disorders or subcortical seizure discharges in patients with convulsive disorders.

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CONCLUDING REMARKS

By R. W. Gerard

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It is significant that this meeting was sponsored jointly by two divisions of The New York Academy of Sciences—Biology and Psychology. This is a unique situation and is indicative of the solvent power of these new drugs in bringing together the body and the mind.

In his introduction, Beckman urged that we pay attention to the etiotropic action, as he well called it, in contradistinction to the action of agents on symptoms. It has also been said that tranquilizers (or ataractic drugs, whichever term will eventually be accepted) make it possible for us to change disturbed mental patients into undisturbed mental patients. Actually, after much discussion we are not even certain whether meprobamate should be regarded as a drug of special interest in relation to mental patients or in a quite different light. This brings me to the first of the four topics I should like to consider: (1) classification, (2) the mechanism of drug action, (3) the problems of testing, and (4) the control of the tension level.

Classification

Classification has been much discussed within these pages and is actually very important in one's orientation; it is not a matter of purely academic interest. As was pointed out by Smith, patients given a drug that has become associated with the treatment of mental disease accept it unhappily, even though they are being treated for some totally unrelated illness. Also, the intellectual context of the agent matters a good deal to the physician. If meprobamate is like aspirin, it can be compared with a certain group of drugs; if it is like chlorpromazine, it is another matter, and it should be compared with a different group of drugs; if it is like mephenesin or zoxazolamine, the situation again is quite different. Greenberg has compared meprobamate in the alcoholic-ward units with morphine and with the barbiturates. Smith has compared it with other muscle relaxants, as has Schlesinger. Reserpine has been compared with one group of agents by one investigator concerned with blood pressure and with another group by another investigator concerned with mental disease. The classification makes a great difference in what one is likely to do or to see, and in the kind of answer obtained.

I remind you of the two priests, addicted to cigars, who were very unhappy over having been prohibited to smoke while participating in the long hours of prayer demanded of them. The two men decided finally that it would do no harm for each to write his bishop and ask for a relaxation of this proscription. One received the answer "no"; the other, the answer "yes." The first had asked, "Is it permissible to smoke while praying?"; the second, "Is it permissible to pray while smoking?"

I do not know what eventual decision will be made as regards the use of these particular drugs, but it will surely be of importance. I suspect that if a given drug finally turns out to be particularly useful in the treatment of psychoses and, therefore, receives the label "tranquilizer," it may help one

million individuals, at most. If the drug turns out to be more valuable in the treatment of neuroses and is given the label "sedative," it may prove useful in six million cases or more. If it turns out that the drug is such a minor agent that it will help only to put people to sleep and is labeled "hypnotic," then it will be used by perhaps twenty million or more people in the United States alone.

Regardless of the practical importance of classification, however, it will do no good to force the issue prematurely. The right terms, in fact the mere existence of terms, must follow the initial development of language, and then of science. I suggest that the words we now use in and out of our professional activities have come into being because, first, someone has noticed a phenomenon in nature; second, he has become sufficiently interested in it to identify it as distinguished from other phenomena and to describe it thus publicly; and, third, he and other persons now interested have communicated to one another their discoveries concerning it with progressively increasing descriptive power. In order to communicate effectively a greater perceptual awareness and discrimination, more and more differentiating words are needed. As is well known, the Eskimos have eighty words describing different states of solid water, while we have only six or eight. Snow and ice have more importance in the Arctic than they have in warmer regions.

So far I have considered the development of language for the discriminative identification of subclasses as one step, but this by itself does not lead to a scientific understanding of the situation. The rudiments of understanding appear when the next step is taken, when some attempt is made to classify or to analyze these different subentities—to put them, at least, into some kind of taxonomic scheme, hopefully, into one that fosters further understanding. As an example of the difference between the two steps, advertisers have taught us a great array of names for different colors. Names are chosen, presumably by practical application of the science of psychology, that will have the greatest possible appeal to women in order to induce the purchase of particular objects. When the wave lengths of any particular color have been established, however, the descriptive term becomes meaningless; as soon as the notion of a spectrum and ordered wave lengths comes into being, the whole collection of terms for color can be replaced by a precise and significant spectral notation. Obviously, therefore, it becomes of the greatest importance to analyze the mechanism of action of these drugs rather than simply to describe their over-all effects.

The Mechanism of Drug Action

I confess to having been astounded at the statement of one clinical participant that the tension that prevents sleep is abolished by the action of meprobamate on the hypothalamus. I was surprised that anyone had found this out so precisely and was able to make a positive statement about it. I was even a little surprised at the more cautious clinician who, in effect, apologized for not being able to answer a question regarding the site of action of meprobamate on the nervous system.

Leo Alexander has made a point worth considering in offering a complex method of distinguishing between anxiety located in the hypothalamus and depression located mainly in the cortex. With this attempt I found myself

in sympathy, as I have made similar efforts in the past and, especially, as Alexander has claimed that his method permits realistic testing. I should even like to suggest the kind of test that would serve in this case. At least one critical action of the mechanism that he described as at work was a negative feedback from the upper to the lower level. Too much anxiety in the lower level fires the upper level, which then inhibits the lower level, so that anxiety tends to be relieved by excess depression. This would mean—if one takes the dangerous liberty of equating mental phenomena with neurophysiological mechanisms—that, where this happens psychologically, appropriate parts of the hypothalamus are being inhibited. In turn, this means that the threshold to a stimulus should be raised there. An indwelling electrode in an appropriate hypothalamic region should then reveal a rise in electrical threshold at the time of depression or anxiety. I say this, of course, in partial jest, but if one does pretend to test hypotheses of this sort objectively, this is how it must be done and, at least in using animals, it is perfectly possible to do so. In fact, my associates and I did just this in studying the action of epinephrine on the central nervous system. Probe electrodes in different regions determined threshold changes—of motor cortex, knee jerk, and hypothalamus—after the administration of various doses of epinephrine.

Nevertheless, this positive statement serves to point out the present negative situation. Even such a serious attempt to find a method that will formalize drug action and lend itself to objective testing on humans is, today, more or less a dream. However desirable such an attempt may be and however fruitful it may ultimately become in accounting for the action of these various agents in terms of their precise mechanisms of influencing the nervous system, at present it would be premature to make any dogmatic statements regarding mechanism. I doubt if anybody knows enough about any drug to have more than a private opinion as to the directions and significance of his laboratory explorations.

Let me exemplify with one "fact," accepted for many years and referred to many times throughout this publication, that seems to me an illegitimate extrapolation from the actual experimental data. I refer to the statement that mephenesin acts by inhibiting interneurons. As far as I know, mephenesin depresses the polysynaptic more than the monosynpatic reflexes. It is possible that it does so by interfering with interneurons; but it is a gross extrapolation of existing knowledge to accept this as a fact in the absence of other evidence. Almost any nonspecific deleterious influence on the spinal cord—low oxygen, low temperature, low sugar, wearing out of the preparation—is likely also to depress the multisynaptic more than the monosynaptic reflexes, and would do so even if all cells and synapses were affected alike. The reflex that requires the most facilitation at some junction would be the first to fail; the more synapses, the more likelihood of this effect. There may be no quantitative difference at all between cells. Many types of neurons do exist in the cord as well as in the brain, and specific drug actions are quite reasonable. I doubt, however, that such an effect has been demonstrated here.

I choose this point, not to denigrate our presumed knowledge, but to emphasize, in a case where even the laboratory scientist has dared to make positive

statements, how careful one must be in drawing such conclusions. In fact, it is precarious even to state that a drug is a stimulant or depressant to the nervous system when the observation is based on a change in total behavior and sometimes even when it is supported by particular observation of the activity—for example, the electrical responses—of one center or another. Recall the simple balance, with a pan on each end and the pointer centered at equality. An increased weight on one side, adding excitation, or a decreased weight on the other, removing inhibition, would tip the pointer to overactivity or "excitation," and the reverse to underactivity or "depression" of total behavior. A drug that stimulates all neurons can add weights on both sides, can tip the scales to convulsions or to coma, depending on whether the action is greater on the excitatory or the inhibitory systems. A drug that is a general depressant can do the same. Without real knowledge of the actual situation, any conclusion as to mechanism is dangerous.

It is even useful to raise the question whether a given drug at different doses always has the same action in varying degree, or can reverse its action, or can act in different ways in different places. At the most general level there is a quantitative gradient along the neuraxis; the upper end is most active metabolically and physiologically—as the pacemaker of the heart is—and the more active regions are knocked out by progressive depression more easily than are the less active areas. Thus anesthetics knock out the "higher" centers before the "vital" centers of the brainstem and so permit anesthesia without death. Hypoglycemia, or low oxygen, also gives a progressive chopping off along the quantitative gradient. On this basis one might think of some drugs as producing effects at the upper end of the nervous system more easily than at the lower end. Relatively speaking, such drugs presumably would modulate the finer nuances of behavior and subjective experience more than they would depress or exaggerate the reflex behavior of the lower part of the nervous system. However, it is equally possible—in fact, it is one of the great hopes of psychopharmacology—that specific chemical agents may differentially activate, depress, or modify the behavior of particular functional systems in the nervous system. If this proves to be the case, such drugs will make fine tools—in contrast to such gross tools of regional lesions or stimulation—for working out the concomitant variations in personality, in symptom complexes, and in clinical entities, and for relating them, ultimately, to particular detailed functional subsystems of the nervous system.

The paper by Baird *et al.*, showing a differential action of the drugs concerned here on various parts of the basal nuclei, is relevant to this point. Quite aside from action at a general level, and without specifically affecting particular parts of the nervous system, a drug may have profound effects simply by altering time relations. This may be the main moral of Hess's paper on imprinting, in which the exciting observation was made that, with drugs, one could delay imprinting—the nervous system of treated ducklings did not imprint at the age of 13 hours, as it normally does, even though the ducklings were wobbling about, but at 20 hours or at some subsequent time. This implies a change in tempo of the maturation process itself. Further, it was suggested that this particular imprinting was merely one stage in the development of the nervous system, that there are specific times for imprinting such characteristics as

docility, mating behavior, decent performance in the herd or, more broadly, socialization, and the like. I wonder if there exist specific kinds of susceptibilities of the nervous system at different times or if the cumulative behavioral capacities allow the fixation of more and more complex patterns.

Let me generalize still further. The whole of biological and psychological development is a series of appropriate reactions to appropriate experiences in the right sequence. Drugs that would simply slow up certain activities or throw them out of phase with others could have tremendous impact on the behavior, even though no particular cell were stimulated or depressed and no particular enzyme were rendered ineffectual or activated. It could all be a disturbance of the patterns rather than the units. This deserves emphasis. If, from a paragraph or even a sentence of type, we drop out all the e's or all the t's, we should probably still be able to read the text without difficulty. Dropping out such a series of letters would be equivalent to knocking out a major enzyme system. If, however, we leave all the letters in any passage, but mix them up, there will be practically no chance of our making any sense of it.

Returning to the problem of gross levels, it has been said that a battery of careful psychological tests given to patients of various kinds has indicated that dexedrine had the same effect as that of a prefrontal leukotomy; chlorpromazine, as that of a cingulate gyrus lesion. I do not know whether these findings will hold up, but this seems to be a useful kind of approach. This is the way, more precisely, to establish a link between the anatomical and physiological on the one side, and the behavioral on the other. At the Mental Health Research Institute last year we tried a similar experiment. Individuals were made hyperthyroid and were returned to normal in the hope that responses to a certain group of psychological tests would change, but that others measuring different parameters of the psyche would not do so. Unfortunately, the results did not show a clear separation.

I should like to consider specifically the question of muscle tone and steadiness, and tremor and anxiety—they do link up physiologically—because they have received so much attention. I remind you that the degree of alertness of an individual, whether awake or asleep, is determined by, among other factors, the degree of muscle tension, and so by the feedback from the muscle proprioceptors and the flow of impulses up to the higher centers. Various agents cause both increased tension and tremor and increased anxiety. One of the best examples is epinephrine itself, which is liberated in association with anxiety and thus can serve as a positive feedback mechanism. Dickel reported, however, that his patients, given meprobamate, showed a substantial decrease in the action potentials of their muscles, but no change in the psychological concomitant of anxiety and worry. Harriet Gillette attempted to analyze the drug action neurophysiologically and to distinguish between pyramidal and extrapyramidal defects—certainly a step in the right direction. She also made inferences that conformed with those of Schlesinger, but with a somewhat less positive final conclusion as to their present usefulness.

I conclude by saying that, although I completely favor experimental analysis of the action of these drugs and regard this as ultimately the necessary and sound way of ascertaining their potentialities, and so of improving the drugs

and their actions, I think we must be very careful not to reach premature and uncertain conclusions. For the time being, those who hold to a statement of what they actually observe—the flaccid feel of a muscle, the occurrence of certain electrical changes, the particular performance of a patient—are likely to contribute most.

I am especially directed toward this conclusion by the exchange between Berger and Pfeiffer, the two pharmacologists who have actually tested meprobamate in some detail on animals. These investigators could not even agree on the actual experimental findings in a number of instances. Obviously a third element will be needed to resolve this. Since one of the disagreements involved the question as to whether patients under meprobamate slept quietly or squirmed around in bed like eels, I could not help but remember the story of the electrophysiologist who led an expedition up the Nile and brought back an electric eel to study. The eel gave shocks nicely for a while, but then grew despondent, slumped in the aquarium, and would not perform. The experimenter had learned something of the eel language and when he asked why, the eel replied, "It is the mating season now, and I am lonesome. I should like another eel." The experimenter, being human as well as scientific, arranged another expedition, and soon a female eel was put in the tank. After a moment of twining ecstasy, however, the two went to opposite sides and the first eel was more despondent than ever. When asked again, "What is wrong? " he said, "Alas, I am A.C. and she is D.C.!"

The Problems of Testing

I shall deal briefly with the problems of testing, since they have been discussed at some length in the recent symposium "The Evaluation of Pharmacotherapy in Mental Illness." Questions raised in this publication that were extensively discussed in that conference include: behavioral toxicity, which does need much emphasis in dealing with behavior-affecting drugs, agents that yield the particular effect desired only at some price, in performance if not in liver function; the problem of transferring to man the results of experiments made on animals; and the influence of a group of patients on the effects of a drug—raised here by Sabshin, Greenberg, and others.

I was impressed by the report of the different relative effects of the drugs on different nursing units. Partly, this seemed related to the severity of the disease, but partly it seemed related also to the unique personalities or individualities of the units. When Greenberg pointed out that, in the alcoholic institute, even placebos gave almost 40 per cent improvement (meprobamate gave twice as much, and the difference was significant statistically) I wondered whether the subjects had been located in the same units. The progressive quieting of the unit, due to the actual soothing of disturbed and disturbing patients by the drug (and obviously easily measurable by a global index, such as the decibels of general noise level of a ward), might have decreased the tensions of those not getting meprobamate, so what was regarded in this case as a placebo effect may have been, so to speak, a reverberation of quiet from the true action of the drug. Similarly, one's own level of conversation fluctuates, depending upon the noise in the room. The installation of soundproofing in a ceiling by itself can lower stress.

At the experimental level of drug testing, the particular problem is that of determining the proper factor for which to look. There is no sense in trying an agent on an animal or on a human who does not manifest the phenomenon the agent is expected to influence. It would have been difficult to find the antibiotic activity of penicillin by giving it only to healthy animals and men. Thus, either the kind of symptom to be influenced must be clearly present or it must be produced. Producing symptoms (convulsions, hallucinations, anxiety) with one drug and then searching for the drugs that will counteract these symptoms is similar to the case of the eminent neurologist who was approached by a patient for treatment of her indigestion. He assured her that he did not treat indigestion, but she insisted that he had been very highly recommended and she wanted him as her doctor. After a long argument he finally said, "I can give you a medicine that produces fits, and I am expert at curing fits."

Next comes the problem of the validation of findings and the relation to dose. On certain phenomena drug action was obtained only at very high doses. This seemed the main import of Hunt's experiments with meprobamate, and equally of Pfeiffer's. On the one hand, laboratory studies indicate that meprobamate is quite inert; on the other hand, a great number of takers seem to experience some benefit, and clinical reports included in these pages—many seemingly well controlled and convincing enough as reported—indicate a definite action. From this one must conclude either that the experimenters have not yet found the right thing to test—which would not be surprising, since we are dealing with agents active on the nuances of complex human behavior for which it is difficult to find electrical or chemical indicators, either in the laboratory or in the patient—or else that the clinical impressions are wrong and that some day these will follow phlebotomy, laudable pus, and other major medical mistakes into the discard. I doubt that the latter is the case, especially because of the genuine awareness of the problem of controls that exists today among the better clinicians and laboratory workers handling these problems.

We have heard much about the double blind and the placebo. The double blind has been described as an experiment in which everybody but the doctor knows what is being given; a report of a double-blind experiment on promazine and chlorpromazine, which act very similarly, supports this definition. The statement was made that the patients knew by the end of the first day whether they were getting *A* or *B*; that the ward attendants and the nurses knew which were which by the end of the second day. Greenberg has stated that, as regards meprobamate and placebo, the case was reversed; doctors, either more intelligent or having more contact with the patients, became aware of the results before the ward attendants did (I do not know whether or not the patients ever did).

A placebo, of course, means something that placates or pacifies or tranquilizes —perhaps we should really use the word "tranquilizer" for the placebos and not for the drugs being tested—but from evidence presented in these pages, they seem to have had a dynamic and exciting influence rather than a pacifying one. In general there has been a tendency to regard placebos in an "all-or-none" fashion and to take hostile positions concerning them. Some statements have been made that I should not have made myself. For example, it is well to compare the unknown agent, not with a completely inactive substance, but

with another agent possessing comparable activity. Here the observer is, so to speak, titrating a smaller difference, and this can be magnified more. Again, the need for using a placebo of any kind depends on the particular situation involved. With a sufficiently objective measure of something not immediately responsive to suggestion (either in the patient or the doctor), it is patently unnecessary to use a placebo. This resembles the situation in the chemical laboratory, where the agent is added to one test tube and not to the other; it is not necessary to add a like amount of water to a third tube just to fool it. Consider the case, described by Schlesinger, of certain patients who, after showing negative results for years on being tested with one after another agent, suddenly responded positively to a new agent. One could be pretty sure, in this case, without using a placebo and barring other significant change, that this agent was active.

The clinical "hunch" must always be the first step, and its earmark is a phrase containing, "I feel," "I believe," "I feel that my patients are helped," or "I believe the drug is doing good." This is the *sine qua non* to further developments. It is what has been called the retail point of view. One is concerned with the individual, accumulates a number of individual cases, and draws conclusions from a consideration of these cases. Without such a conviction one would never know what kind of exact tests to make or what things to look for when the drugs are administered. So there is no conflict between this and the other type of approach, that of the experimentalist and that of the statistician or actuary—the wholesale point of view. The experiments and statistics of the objective scientist are just as necessary in verifying a hunch as clinical art is necessary in its inception. I assure you that getting the right hunch is by far the more creative part of the job; but testing the hunch is by far the most important part and the one requiring the greatest expenditure of time and care.

My own impression from the papers, particularly on the clinical side, is that meprobamate does act strongly on what might be called symptomatically (I here may violate some *caveats* I made earlier) the tension level. This level helps control stress or decrease tension, whether in terms of lessened downward discharges to muscles and easing of spasticity, of lessened discharges upward to the cortex (or the psyche or superego) with an easing of hostility, directed outward or inward, of anxiety, or of some other factor.

Control of Tension Level

Enthusiasm over the action of meprobamate in making patients co-operative has been expressed in a number of papers. Senile, alcoholic, and other sad relics, who would not accept help from willing and friendly ward personnel, abandoned their stubborn resistance. This is obviously a good and helpful effect and indicates a valid use for any drug that can produce it. One could, however, as implied by Huxley, use another word for "co-operative." One could say the drug makes people docile, renders them susceptible to outer influences, including the "big brother" variety and brain washing. As Dickel asks, what are the criteria that one should consider in judging effective therapeutic results of a drug? They include not only the feelings of the patient,

but also his performance in the community, whether or not he can hold a job and interact with his fellows.

Two basic antinomies arise here: the conflict within the individual, between the desire for nirvana and the desire for experience; and the conflict between the individual and the group, for the peace of the individual and the progress of the society or species. As far as the group is concerned—and I should use here the term "epiorganism"—it is certainly true that, throughout evolution, selection of individuals to be parents for the next generation has had nothing to do with the welfare of those individuals. In most cases the selection has been an entirely painless one in terms of slight advantages in adaptive mechanisms but, in many situations, the individuals are ruthlessly sacrificed for the good of the group.

This is really the theme of the legend of Prometheus, who stole fire from heaven. He brought progress for mankind but, as an individual, he suffered the tortures of being torn by ravens. The conflict between the individual and the group also underlies the ethical problem in human experimentation that has been aired here. Is it ever ethically permissible to withhold from a patient that treatment which, at the moment, is regarded as the best and most satisfactory? If not, how could one test the new, or give placebos to controls, or try uncertain remedies? Conversely, under what conditions is it desirable or ethically permissible to try on a patient something that may be better than the current agent but which may also prove harmful? When does one stop using the good in an effort to achieve the better? This is a very basic ethical problem and it bothers all who operate in this field, not only morally, but even legally. It is not easy to answer the question: "What calculated risk is permissible with a given human individual for a potential great gain to mankind as a whole?" I do not presume to resolve this problem; I simply state it.

Turning, finally, to conflict within the individual, there are a number of interesting points. Consider the new techniques of allowing monkeys with indwelling electrodes in the brain to give themselves shocks. If the electrode is in a region associated with painful experience, an animal presses the lever once, jumps, and never touches it again. If the electrodes are elsewhere, however, in the limbic system and its adnexae, the animal is likely to continue punching the lever for long periods, and will even undergo some external discomfort in order to do this. The question arises "What does he get out of it?" There has been a tendency, with some justification for certain regions of the brain, to think that the shocks arouse the equivalent of sexual feelings; if such feelings can be produced centrally, without wearing out the peripheral mechanism, continuing elicitation is understandable. It may not be as simple as this, however; there is some reason to believe that, rather than pleasurable experience, the stimuli may give only nirvana. Children with *petit mal*, who can bring on an attack with a flickering light, may spend hours in the sunshine waving their fingers before their eyes and having attack after attack. They behave in many respects like the monkeys; conversely, the monkey behavior is perhaps directed to a negative effect. Are these animals seeking a positive pleasure or a negative absence of experience? Here, at least, is a technique only beginning to be exploited that may lead to many clear-cut answers to such questions.

More immediately I remind you that, both in the evolution of the species and in the development of the individual, with the increase of the functioning cortex there is a progressive emergence of what Kleitman called the wakefulness of choice as compared to the wakefulness of necessity. This goes back to W. R. Hess's experiments three decades ago. Animals sleep and are inactive except when they must do something about solving the problems of life. This is the wakefulness of necessity. With the growth of the cortex there is more and more of the additional wakefulness of choice—an extra libido; in Alexander's view, the play libido—a desire or the ability to keep going, to be active for activity's sake, a *joie de vivre*, a joy of play.

Huxley has made the point that all natural depressant drugs, tranquilizers or whatever one may call them, have been known from antiquity. This is certainly true. He did not suggest, however, that all the natural drugs that give increased activity, that move one away from a state of peace and nirvana, were also discovered in antiquity. Indeed, as far as I know, these are much more widely sought and used in every culture than are the depressants. As regards primitive or advanced groups, coffee, tea, or maté, wherever available, is the main beverage of the people; the cup that cheers takes precedence over the cup that inebriates. I have some apprehension at Huxley's suggestion that we try to teach children to control their autonomic nervous systems. It took organisms a long time to exclude these actions from voluntary control, so that the fools could not kill themselves off at once. By way of answering Huxley's concluding question, I rather suspect that, even though we are now tampering with the upper part of our nervous system, we shall survive without serious damage.

There is certainly something like an *élan vital* effective in all living creatures, pointed up in man as a "divine unrest." Biology would give a positive answer to the question that the poets and the humanists have raised and have answered in all possible ways and nuances. The biologist stands with Louis Untermeyer rather than with Swinburne, and therefore subscribes to the second of these verses:

"From too much love of living,
From hope and fear set free,
We thank with brief thanksgiving
Whatever gods may be
That no life lives for ever;
That dead men rise up never;
That even the weariest river
Winds somewhere safe to sea."

"From compromise and things half-done,
Keep me, with stern and stubborn pride;
And when, at last, the fight is won,
God, keep me still unsatisfied."

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